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PATENT ABSTRACTS OF JAPAN

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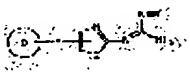
(71)Applicant : ONO PHARMACEUT CO LTD
(72)Inventor : MATSUI TOSHIAKI
TATSUMI TADASHI
OUCHIDA SHUICHI

(54) GUANIDYL DERIVATIVE

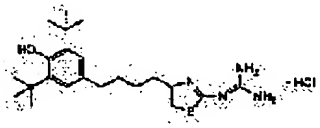
(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a new guanidyl derivative, having excellent suppressing actions on the Maillard reaction and antioxidant actions in combination and further high safety and useful for treatment and/or prevention of diabetic complications, atherosclerosis, etc.
SOLUTION: This guanidyl derivative of formula I {Z is S, O or NR2 (R″ is H or a 1–4C alkyl); R1 is H, a 1–4C alkyl or a 2–5C acyl; A is a single bond, a 1–8C alkylene, etc.; ring D group is a group of formula II [R3 is H, a 1–4C alkyl or a 2–5C acyl; (l) is 0 or 1–10; R4 is a 1–4C alkyl; (p) is 0 or 1–2], formula III [R5 is a 1–7C alkyl, a halogen, etc.; (m) is 0 or 1–5] or formula IV [R7 is a 1–7C alkyl, phenyl, etc.; (n) is 0 or 1–3, etc.]} or its acid addition salt, e.g. a compound of formula V is cited. For example, the compound of formula V is obtained by using a compound prepared from a 3,5–di–t–butyl–4– hydroxybenzaldehyde and methyl triphenylphosphoranylideneacetate as a starting raw material through several steps.


I


II


III


IV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LEGAL STATUS

[Date of request for examination]

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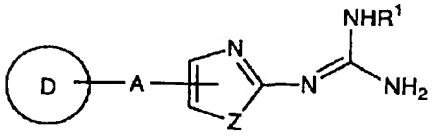
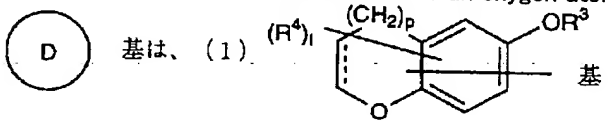
CLAIMS

[Claim(s)]
[Claim 1] A general formula (I)
[Formula 1]

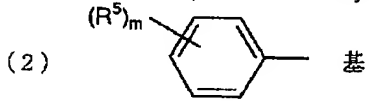


(I)

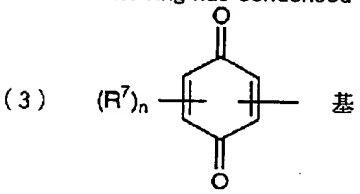
(Z expressing a sulfur atom, an oxygen atom, or NR2 (R2 expressing a hydrogen atom or the alkyl group of C 1-4 among a radical.) among a formula, R1 expressing a hydrogen atom, the alkyl group of C 1-4, or the acyl group of C 2-5, and A expressing single bond, the alkylene group of C 1-8, and the alkylene group of C 2-8 to which one carbon atom is replaced with one sulfur atom or an oxygen atom.) [Formula 2]



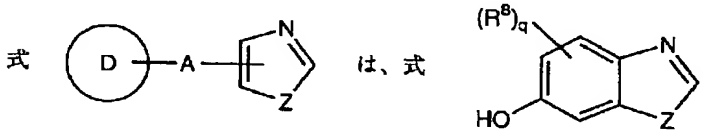
(— R3 expresses a hydrogen atom, the alkyl group of C 1-4, or the acyl group of C 2-5 among a radical, l expresses 0, or 1-10, R4 expresses the alkyl group of C 1-4, and p expresses 0, or 1-2.) [Formula 3]



the inside of a radical and R5 are the alkyl group of C 1-7, and six OR (the inside of a radical, and R6 — a hydrogen atom —) the alkyl group of C 1-4, the acyl group of C 2-5, a phenyl group, or phenyl-C1 - 4 alkyl groups is expressed. a halogen atom, a phenyl group or phenyl-C1 - 4 alkyl groups, the cycloalkyl radical of C 5-7, or cycloalkyl-C1 of C 5-7 - 4 alkyl groups is expressed, and m expresses 0, or 1-5. or the above-mentioned ring which the benzene ring has condensed — or [Formula 4]



(— R7 expresses the alkyl group of C 1-7, a phenyl group or phenyl-C1 - 4 alkyl groups, the cycloalkyl radical of C 5-7, or cycloalkyl-C1 of C 5-7 - 4 alkyl groups among a radical, and n expresses 0, or 1-3.) — it expresses. moreover [Formula 5]



(— R8 expresses the alkyl group of C 1-7, a phenyl group or phenyl-C1 - 4 alkyl groups, the cycloalkyl radical of C 5-7, or cycloalkyl-C1 of C 5-7 - 4 alkyl groups among a formula, and q expresses 0, or 1-3.) — it expresses. However, a sulfur atom or an oxygen atom among (i) A [Formula 6]

It is alike and does not join together directly (ii).

[Formula 7]

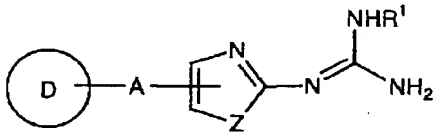
In ** (1), a sulfur atom or an oxygen atom among A [Formula 8]

It is alike and does not join together directly. The guanidyl derivatives shown, those acid addition salts.

[Translation done.]

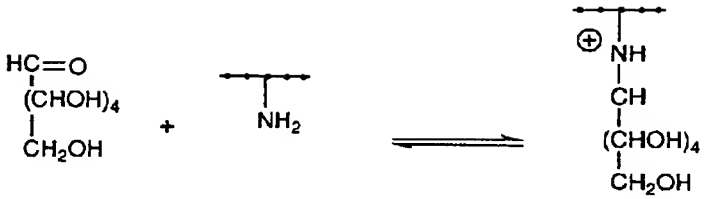
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to a guanidyl derivative useful as physic. If it says in more detail, this invention will be one general formula (I).
[Formula 9]

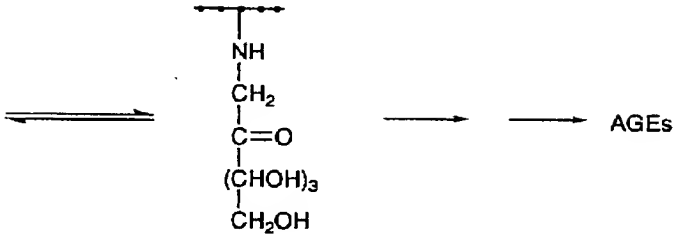


(I)

(-- all marks express the same semantics as a postscript among a formula.) -- the guanidyl derivatives shown, those acid addition salts, and 2 -- those manufacture methods and 3 -- it is related with the drugs which contain them as an active principle.
[0002]
[Background of the Invention] Maillard (Maillard) reported in 1912 paying attention to the phenomenon colored brown, when the mixture of amino acid and reducing sugar was heated [Maillard, L.C., Compt.Rend.Soc.Bio., 72, and 599] (1912). This is based on the reaction of amino acid and sugar, and it suggested that this reaction might occur after that even in the living body. It continued till 1968 and reported that HbA1c which is the small component of hemoglobin increased RABA (Rahbar) in a diabetic [Rahbar.S., Clin.Chim.Acta., 22, and 296] (1968). Combining [with behind]-with mold in which glucose carried out AMADORI (Amadori) rearrangement to beta chain amino terminal valine-the chemical structure of this HbAIc [Koenig, R.J., Blobstein, S.H., & Cerami, A., and J. Biol.Chem., 252, 2992 (1977)], and this reaction -- being nonenzymatic (nonenzymatic) -- happening [Stevens, V.J., Vlassara, H., Abati, A., & Cerami, A., J.Biol.Chem., and 252 -- 2998 (1977)] etc. was clarified. It was checked that the Maillard reaction has occurred in the living body.
[0003] As for a Maillard reaction, the amino group of reducing sugar and protein starts glycosylation (glycosylation) first as the initial stage to form a lifting and an Amadori rearrangement product. if this advances further -- protein -- bridge formation polymerization [-- this polymerization object is called glycosylation product (it is written as Advanced Glycosylation End products;AGE.) which advanced.] It carries out and the solubility falls, it is hard coming to win popularity an operation of a protease, fluorescence occurs soon, and it colors brown. Although various mechanisms of AGE generation are advocated, according to Brown Lee and others (Brownlee), it is as follows, for example (Brownlee, M.et al., Science, 232, and 1629 (1986)).
[0004]
[Formula 10]



グルコース　　プロテイン　　シッフ塩基



アマドリ転位生成物

[0005] Although a Maillard reaction is a phenomenon seen also in healthy people, in the diabetic to whom the blood sugar level rises, and the late protein part of metabolic turnover, it sees notably. For example, at hemoglobin, a diabetes-mellitus mouse is 2.7 of a normal mouse. Glycosylation of twice has taken place and also set [Monnier, V.M.et al., the Maillard Reaction in Foods and Nutrition, ACS Symposium Series, 215, 432, Am.Chem.Soc. and Washington D.C.] (1983) and serum albumin to a diabetic. ** glycosylation is accelerating [Guthrow and C.E.et al., Proc.Natl.Acad.Sci.U.S.76, and 4258] (1979). typical diabetic kidney trouble appears with injecting intravenously to a mouse the serum protein furthermore glycosylated over 12 weeks of repeats — [Monnier, V.M.et al., Clin.Endocrinol.Metab., 11, and 431] (1982) have become clear.

[0006] Once a biosynthesis is carried out, they are crystallin ** of an eyeball lens, and special protein which does not carry out metabolic turnover at all. When this crystallin ******** glycosylation took place, it was admitted that change arises in a spacial configuration, an enzyme participates in an intramolecular sulfhydryl group, and an S-S bond was formed and macromolecule-ized. In the case of the diabetes-mellitus student cataract of a rat, association with a glucose reaches also 10 normal times, and an intramolecular S-S bond also increases it [Monnier, V.M.& Cerami, A.Clin, Endocrinol.Metab, 11, and 431] (1982).

[0007] A polymerization, insolubilization, fluorescence generating, and coloring of yellow - brown have taken place with glycosylation of KURISUTARIN, and such change coincides with change of the lens by aging well [Chiou, S.H., Chylack, L.T.Jr., Tung, W.H., & Bunn, F., J.Biol.Chem.256, and 5176] (1981).

[0008] It is protein which is rich in a lysine and hydroxylysine, and metabolic turnover is also late, existence of a connective with a glucose is found out by mesangium basement membrane, ******, etc., and the collagen which exists in a connective tissue, and an elastin are [Monnier and V.M., Stevens, V.J., & Cerami, A., Maillard Reactions in Food, Prog.Food Nutr.Sci.5, 315, Pergamon Press, London], [Rosenburg, H., Modrak and J.B. which are considered that there is relation also in hardening of a blood vessel wall, Hassing, J.M., aluminum-Turk, W.A., & Stohs, S.J., and Biochem.Biophys. Res.Commun., 91, 498 (1979)]. Moreover, nonenzymatic glycosylation of nerve myelin protein can be considered as a cause of a diabetic nervous disease [Monnier, V.M.et al., Clin.Endocrinol.Metab.11, and 431] (1982).

[0009] Thus, it is thought that the Maillard reaction is participating not only in diabetic various complication but in the various diseases accompanying aging (aging). Moreover, it is reported by the latest research that the free radical may be participating in glycosylation of protein [Diabete & Metabolism (Paris), 14, and 25-30 (1988)].

[0010]

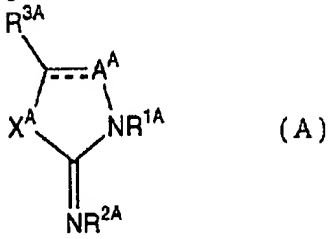
[Description of the Prior Art] Retrieval of the material which checks a Maillard reaction recently is performed on the basis of the above backgrounds. For example, Brown Lee and others showed that aminoguanidine prevents a Maillard reaction in in vitro (inch vitro) one, and that generation of AGE in an artery wall would be controlled if a diabetes-mellitus rat is further medicated with aminoguanidine [Brownlee, M.et al., Science, 232, and 1629] (1986). And the amino group (it combined with the guanidino radical) of the aminoguanidine which is a nucleophilicity hydrazine compound as the operation mechanism blocks the activity carbonyl group in an Amadori rearrangement product, and suppose that it is it for preventing that the bridge formation polymerization of the Amadori rearrangement product is carried out further.

[0011] Furthermore the constituent which controls generation of the secondary glycosylation end product which consists of a compound which has an activity carbonyl group in an Amadori rearrangement product and the active-nitrogen content radical (amino group combined with the guanidino radical) which can react on

JP,62-142114,A specifications is suggested, and aminoguanidine, alpha-hydrazino histidine, and the lysine are specifically indicated.

[0012] Moreover, in a JP,7-133264,A specification, it is a general formula (A).

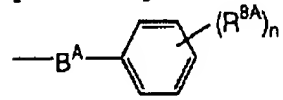
[Formula 11]



(A)

[0013] inside of formula, and R1A — a hydrogen atom, a low-grade alkoxy carbonyl low-grade alkyl group, etc. Expressing, R2A is the amino group, a substitute phenyl sulfonylamino radical, or -N=R4A set (among a radical). R4A expresses a low-grade alkylidene radical, a low-grade cyclo alkylidene radical, a phenyl low-grade alkylidene radical, etc. It expresses. R3A A hydrogen atom, low-grade alkyl group, and low-grade alkenyl radical, A phenyl low-grade alkoxy low-grade alkyl group, the phenyl group which has had the hydroxyl group, The partial saturation low-grade heterocycle low-grade alkyl group of 5 members or 6 members, -N(R6A) R7A set (among a radical) R6A expresses a low-grade alkyl group and carboxy low-grade alkyl group, low-grade alkoxy carbonyl low-grade alkyl group, 6-hydroxy-2, 5 and 7, and 8-tetramethyl-2-chromanyl-methyloxy radical etc., and R7A expresses a hydrogen atom or a low-grade alkyl group. or [0014]

[Formula 12]



基

(— BA expresses a low-grade alkylene group among a radical; R8A expresses a hydroxyl-group, nitro group, amino-group, halogen atom, low-grade alkyl group, lower alkoxy group, phenoxy group, phenyl low-grade alkyl group, low-grade alkylthio group, and phenyl low-grade alkylthio group etc., and n expresses 0, or 1-3.) — expressing — XA -S- or -N(R10A)- (R10A expresses a hydrogen atom or a low-grade alkoxy carbonyl low-grade alkyl group.) — expressing [0015]

[Formula 13]

When it expresses ********, AA expresses a carbonyl group, [Formula 14]

When it expresses **********, AA expresses =C(R11A)- (R11A expresses a low-grade alkyl group and low-grade alkoxy carbonyl low-grade alkyl group etc.). The compound shown is indicated as a Maillard reaction inhibitor.

[0016]

[Objects of the Invention] this invention persons had the depressant action which was excellent to the Maillard reaction, and it inquired in order to find out a new compound with high safety, and the guanidyl derivative shown by the general formula (I) found out attaining the purpose. Moreover, that this derivative also has an antioxidation operation also found out.

[0017]

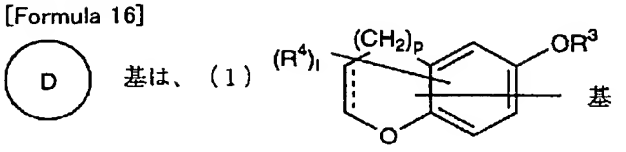
[Description of the Prior Art] The guanidyl derivative of this invention compound is a new compound which is not known at all until now. When it explains in detail, the compound shown by the formula (A) is a compound which has a thiazole or an imidazole ring among the conventional technology. However, the radical replaced by the 2nd place of those rings is hydrazino (when R2A is an amino group) or a substitute hydrazino radical (when R2A is a substitute phenyl sulfonylamino radical or -N=R4A). It is the compound with which this invention compound makes a guanidyl radical indispensable to it at the 2nd place of a thiazole, oxazole, or an imidazole ring. Therefore, this invention compound can be said to be that the compound shown by the formula (A) is a compound which has completely different structure. Moreover, it can be said that this invention compound differs from the compound shown by said formula (A) also from the point of having an antioxidation operation.

[0018]

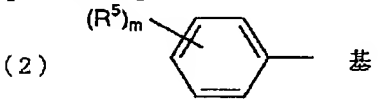
[Description of the Invention] This invention is one general formula (I).

[Formula 15]

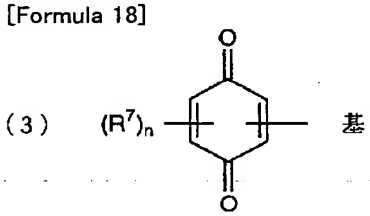
carbon atom is replaced with one sulfur atom or an oxygen atom.) [0020]
[Formula 16]



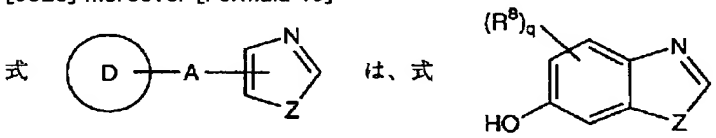
(— R3 expresses a hydrogen atom, the alkyl group of C 1–4, or the acyl group of C 2–5 among a radical, l expresses 0, or 1–10, R4 expresses the alkyl group of C 1–4, and p expresses 0, or 1–2.) [0021]
[Formula 17]



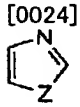
(The inside of a radical and R5 are the alkyl group of C 1–7, and six OR (the inside of a radical and R6 are a hydrogen atom, the alkyl group of C 1–4, the acyl group of C 2–5, a phenyl group, or phenyl – [C1 – 4 alkyl groups are expressed.]).) a halogen atom, a phenyl group or phenyl–C1 – 4 alkyl groups, the cycloalkyl radical of C 5–7, or cycloalkyl–C1 of C 5–7 – 4 alkyl groups is expressed, and m expresses 0, or 1–5. or the above–mentioned ring which the benzene ring has condensed — or [0022]
[Formula 18]



(— R7 expresses the alkyl group of C 1–7, a phenyl group or phenyl–C1 – 4 alkyl groups, the cycloalkyl radical of C 5–7, or cycloalkyl–C1 of C 5–7 – 4 alkyl groups among a radical, and n expresses 0, or 1–3.) — it expresses.
[0023] moreover [Formula 19]



(— R8 expresses the alkyl group of C 1–7, a phenyl group or phenyl–C1 – 4 alkyl groups, the cycloalkyl radical of C 5–7, or cycloalkyl–C1 of C 5–7 – 4 alkyl groups among a formula, and q expresses 0, or 1–3.) — it expresses.
[0024] However, a sulfur atom or an oxygen atom among (i) A [Formula 20]



It is alike and does not join together directly (ii).
[Formula 21]

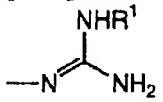
In ** (1), a sulfur atom or an oxygen atom among A [Formula 22]

it is alike and does not join together directly the guanidyl derivatives shown, those acid addition salts, and 2 — those manufacture methods and 3 — it is related with the drugs which contain them as an active principle.
[0025] The alkyl groups of C 1–4 shown by R1, R2, R3, R4, and R6 are methyl, ethyl, propyl, butyls, and these isomer radicals among a general formula (I). The acyl groups of C 2–5 shown by R1, R3, and R6 are acetyl, a propionyl, the butyryl, valeryl radicals, and these isomer radicals among a general formula (I). Phenyl shown by R5, R6, R7, and R8 among a general formula (I) – C1 – 4 alkyl groups are the methyl replaced by one phenyl group, ethyl, propyl, butyls, and these isomer radicals. The alkyl groups of C 1–7 shown by R5, R7, and R8 are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl radicals, and those isomer radicals among a general formula (I).
[0026] The alkylene groups of C 1–8 shown by A are methylene, ethylene, trimethylene, tetramethylen, pentamethylene, hexamethylene, heptamethylene, octamethylene radicals, and these isomer radicals among a general formula (I). With the alkylene group of C 2–8 by which one carbon atom shown by A replaced one sulfur atom or an oxygen atom, one carbon atom in ethylene, trimethylene, tetramethylen, pentamethylene, hexamethylene,

heptamethylene, octamethylene radicals, and these isomer radicals replaces a sulfur atom or one oxygen atom among a general formula (I). As a halogen atom shown by R5, a fluorine, chlorine, a bromine, and iodine are mentioned among a general formula (I).

[0027] In this invention, it points especially in the inside of a specification, and a structure expression, and as long as there is nothing, an isomer includes this all. For example, the thing of a straight chain and the thing of a branched chain are contained in an alkyl group, an alkylene group, and an alkenylene group, and the double bond under double bond in an alkenylene group contains what is E, Z, and EZ mixture. Moreover, the isomer produced by existence of asymmetric carbon atoms in case the alkyl group of a branched chain exists is also contained.

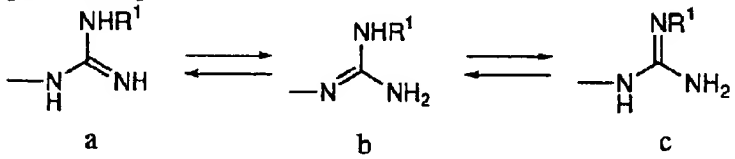
[0028] Moreover, inside of this invention, [Formula 23]



It comes out, and as the radical shown is shown below, a tautomerism exists.

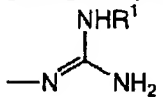
[0029]

[Formula 24]



a b c

[0030] It depends, [Formula 25]



It comes out and the radical shown expresses all the above-mentioned radicals of a, b, and c.

[0031]

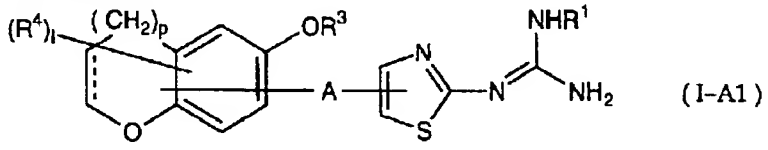
[Salt] The compound shown by the general formula (I) is changed into an acid addition salt by request by the well-known method. As for an acid addition salt, it is desirable that they are nontoxic and water solubility. As a suitable acid addition salt, a hydrochloride, the hydrobromate, a hydroiodic-acid salt, a sulfate, phosphate, an inorganic-acid salt like a nitrate or acetate, a lactate, a tartrate, a benzoate, citrate, a methansulfonic acid salt, an ethane-sulfonic-acid salt, a benzenesulfonic acid salt, a toluenesulfonic acid salt, an isethionic acid salt, a glucuronic acid salt, and an organic-acid salt like gluconate are mentioned, for example. An acid addition salt is obtained by making the compound shown by the general formula (I) react the amount of theories every with a desired acid in a well-known method, for example, a suitable solvent.

[0032]

[The concrete compound of this invention] As a desirable compound of this invention, the following general formulas (I-A1), (I-A2), (I-A3), (I-A4), (I-B1), (I-B2), (I-B3), (I-B4), (I-C1), (I-C2), (I-C3) or (I-C4) the compound shown, and the compound of an example are mentioned.

[0033]

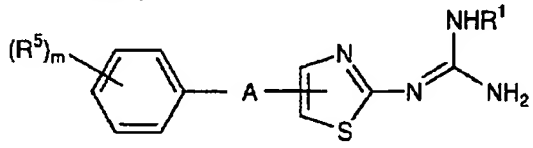
[Formula 26]



(I-A1)

[0034]

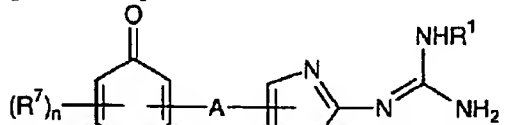
[Formula 27]



(I-A2)

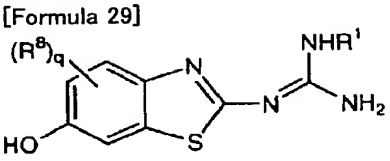
[0035]

[Formula 28]



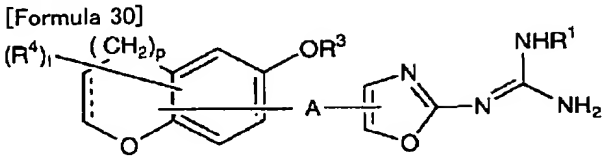
(I-A3)

[0036]
[Formula 29]



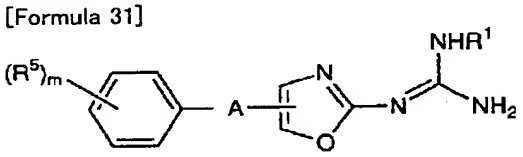
(I-A4)

[0037]
[Formula 30]



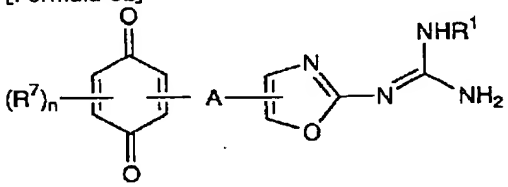
(I-B1)

[0038]
[Formula 31]



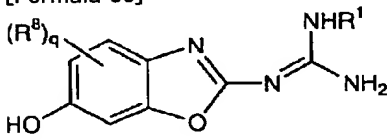
(I-B2)

[0039]
[Formula 32]



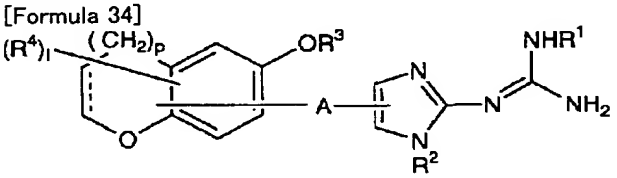
(I-B3)

[0040]
[Formula 33]



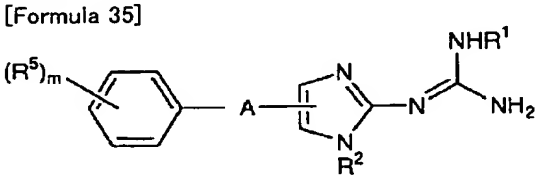
(I-B4)

[0041]
[Formula 34]



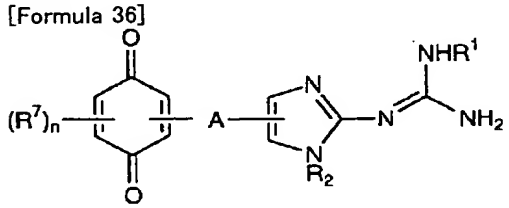
(I-C1)

[0042]
[Formula 35]



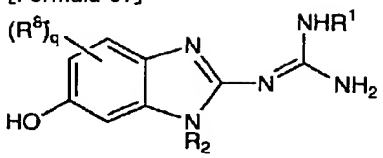
(I-C2)

[0043]
[Formula 36]



(I-C3)

[0044]
[Formula 37]

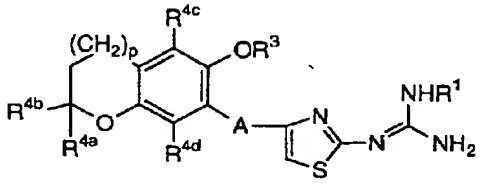


(I-C4)

[0045] As a concrete compound, the compound shown with the following tables 1-24 and the compound of an example are mentioned. In addition, Me expresses a methyl group among a table, t-Bu expresses tertiary butyl, Ph expresses a phenyl group, and Bz expresses benzyl.

[0046]
[A table 1]

表1

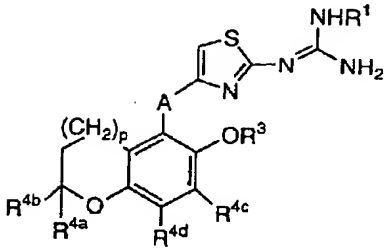


(I-A11)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0047]
[A table 2]

表2

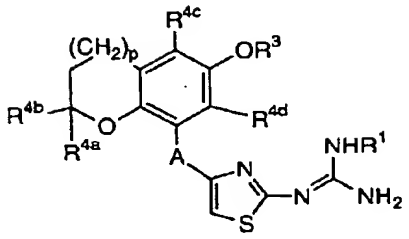


(I-A12)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0048]
[A table 3]

表3

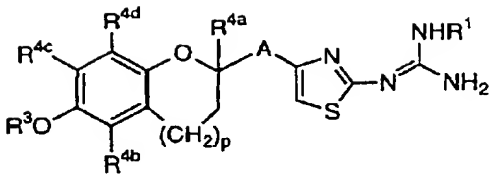


(I-A13)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0049]
[A table 4]

表4

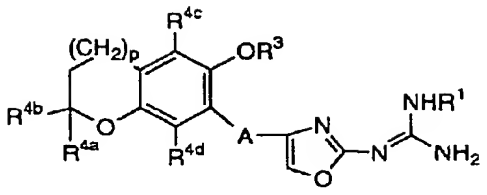


(I-A14)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0050]
[A table 5]

表5

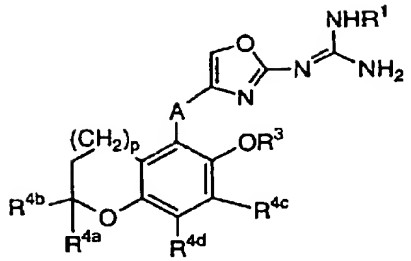


(I-B11)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0051]
[A table 6]

表6

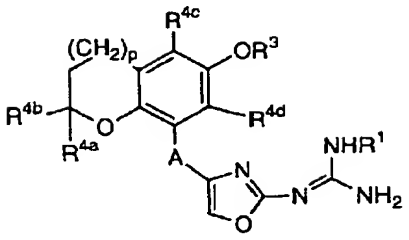


(I-B12)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0052]
[A table 7]

表7

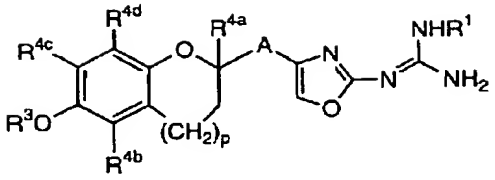


(I－B13)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0053]
[A table 8]

表8

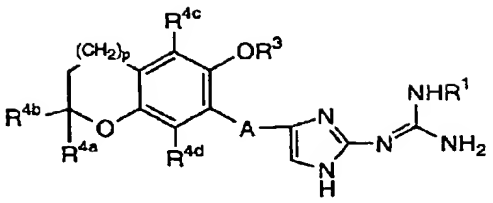


(I-B14)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0054]
[A table 9]

表9

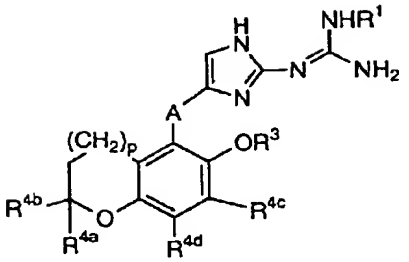


(I-C11)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0055]
[A table 10]

表１０

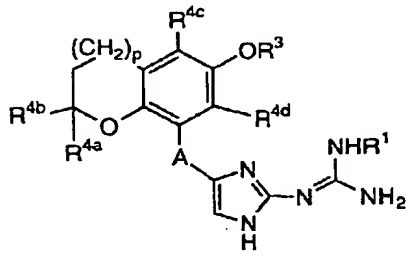


(I-C12)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0056]
[A table 11]

表１１

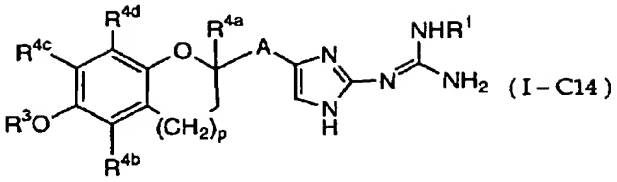


(I－C13)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0057]
[A table 12]

表１２

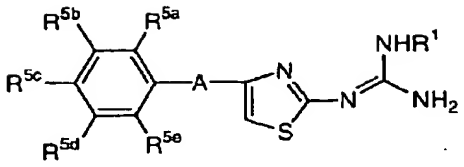


(I-C14)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

[0058]
[A table 13]

表１３

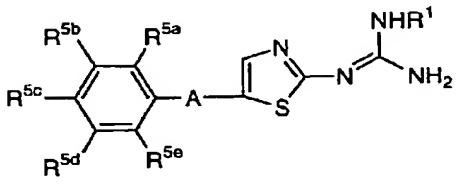


(I－A21)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_2-$
2	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_2-$
3	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_2-$
4	H	H	H	t－Bu	H	H	$-(CH_2)_2-$
5	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
6	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
7	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_4-$
8	Me	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
9	Me	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_2-$
17	H	H	t－Bu	OMe	t－Bu	H	$-S(CH_2)_2-$
18	H	H	t－Bu	H	t－Bu	H	$-S(CH_2)_4-$
19	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_4-$
20	H	H	t－Bu	H	t－Bu	H	$-O(CH_2)_4-$

[0059]
[A table 14]

表１４

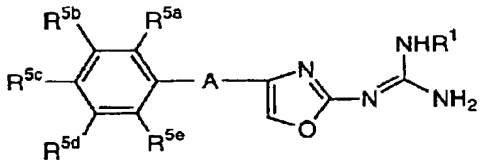


(I-A22)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t−Bu	OH	t−Bu	H	$-(CH_2)_2-$
2	H	H	t−Bu	OMe	t−Bu	H	$-(CH_2)_2-$
3	H	H	t−Bu	H	t−Bu	H	$-(CH_2)_2-$
4	H	H	H	t−Bu	H	H	$-(CH_2)_2-$
5	H	H	t−Bu	OH	t−Bu	H	$-(CH_2)_4-$
6	H	H	t−Bu	OMe	t−Bu	H	$-(CH_2)_4-$
7	H	H	t−Bu	H	t−Bu	H	$-(CH_2)_4-$
8	Me	H	t−Bu	OH	t−Bu	H	$-(CH_2)_4-$
9	Me	H	t−Bu	OMe	t−Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t−Bu	OH	t−Bu	H	$-S(CH_2)_2-$
17	H	H	t−Bu	OMe	t−Bu	H	$-S(CH_2)_2-$
18	H	H	t−Bu	H	t−Bu	H	$-S(CH_2)_4-$
19	H	H	t−Bu	OH	t−Bu	H	$-S(CH_2)_4-$
20	H	H	t−Bu	H	t−Bu	H	$-O(CH_2)_4-$

[0060]
[A table 15]

表１５

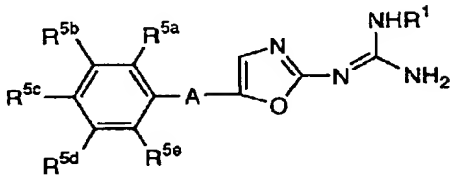


(I－B21)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_2-$
2	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_2-$
3	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_2-$
4	H	H	H	t－Bu	H	H	$-(CH_2)_2-$
5	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
6	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
7	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_4-$
8	Me	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
9	Me	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_2-$
17	H	H	t－Bu	OMe	t－Bu	H	$-S(CH_2)_2-$
18	H	H	t－Bu	H	t－Bu	H	$-S(CH_2)_4-$
19	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_4-$
20	H	H	t－Bu	H	t－Bu	H	$-O(CH_2)_4-$

[0061]
[A table 16]

表１６

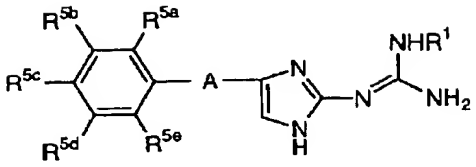


(I－B22)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_2-$
2	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_2-$
3	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_2-$
4	H	H	H	t－Bu	H	H	$-(CH_2)_2-$
5	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
6	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
7	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_4-$
8	Me	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
9	Me	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_2-$
17	H	H	t－Bu	OMe	t－Bu	H	$-S(CH_2)_2-$
18	H	H	t－Bu	H	t－Bu	H	$-S(CH_2)_4-$
19	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_4-$
20	H	H	t－Bu	H	t－Bu	H	$-O(CH_2)_4-$

[0062]
[A table 17]

表１７

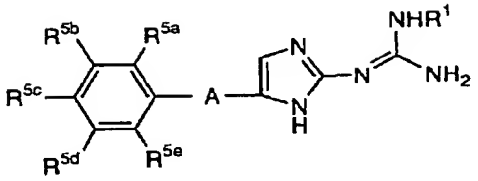


(I-C21)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t−Bu	OH	t−Bu	H	$-(CH_2)_2-$
2	H	H	t−Bu	OMe	t−Bu	H	$-(CH_2)_2-$
3	H	H	t−Bu	H	t−Bu	H	$-(CH_2)_2-$
4	H	H	H	t−Bu	H	H	$-(CH_2)_2-$
5	H	H	t−Bu	OH	t−Bu	H	$-(CH_2)_4-$
6	H	H	t−Bu	OMe	t−Bu	H	$-(CH_2)_4-$
7	H	H	t−Bu	H	t−Bu	H	$-(CH_2)_4-$
8	Me	H	t−Bu	OH	t−Bu	H	$-(CH_2)_4-$
9	Me	H	t−Bu	OMe	t−Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t−Bu	OH	t−Bu	H	$-S(CH_2)_2-$
17	H	H	t−Bu	OMe	t−Bu	H	$-S(CH_2)_2-$
18	H	H	t−Bu	H	t−Bu	H	$-S(CH_2)_4-$
19	H	H	t−Bu	OH	t−Bu	H	$-S(CH_2)_4-$
20	H	H	t−Bu	H	t−Bu	H	$-O(CH_2)_4-$

[0063]
[A table 18]

表１８

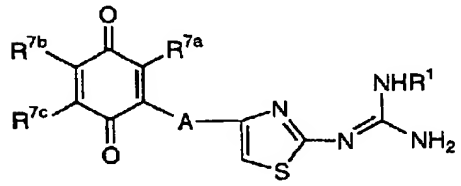


(I-C22)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t−Bu	OH	t−Bu	H	$-(CH_2)_2-$
2	H	H	t−Bu	OMe	t−Bu	H	$-(CH_2)_2-$
3	H	H	t−Bu	H	t−Bu	H	$-(CH_2)_2-$
4	H	H	H	t−Bu	H	H	$-(CH_2)_2-$
5	H	H	t−Bu	OH	t−Bu	H	$-(CH_2)_4-$
6	H	H	t−Bu	OMe	t−Bu	H	$-(CH_2)_4-$
7	H	H	t−Bu	H	t−Bu	H	$-(CH_2)_4-$
8	Me	H	t−Bu	OH	t−Bu	H	$-(CH_2)_4-$
9	Me	H	t−Bu	OMe	t−Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t−Bu	OH	t−Bu	H	$-S(CH_2)_2-$
17	H	H	t−Bu	OMe	t−Bu	H	$-S(CH_2)_2-$
18	H	H	t−Bu	H	t−Bu	H	$-S(CH_2)_4-$
19	H	H	t−Bu	OH	t−Bu	H	$-S(CH_2)_4-$
20	H	H	t−Bu	H	t−Bu	H	$-O(CH_2)_4-$

[0064]
[A table 19]

表１９

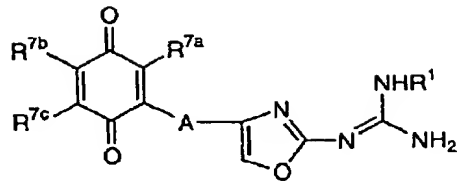


(I-A31)

	R^1	R^{7a}	R^{7b}	R^{7c}	A
1	H	Me	Me	Me	$-(CH_2)_2-$
2	Me	Me	Me	Me	$-(CH_2)_2-$
3	H	Me	Me	Me	$-(CH_2)_4-$
4	H	Me	Me	Me	$-S(CH_2)_4-$
5	H	Me	Me	Me	$-O(CH_2)_4-$

[0065]
[A table 20]

表２０

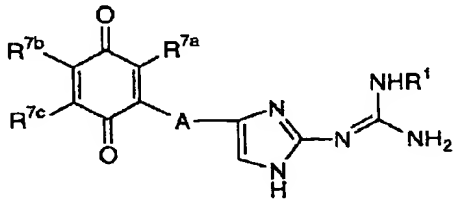


(I－B31)

	R^1	R^{7a}	R^{7b}	R^{7c}	A
1	H	Me	Me	Me	$-(CH_2)_2-$
2	Me	Me	Me	Me	$-(CH_2)_2-$
3	H	Me	Me	Me	$-(CH_2)_4-$
4	H	Me	Me	Me	$-S(CH_2)_4-$
5	H	Me	Me	Me	$-O(CH_2)_4-$

[0066]
[A table 21]

表２１

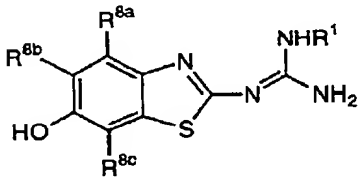


(I－C31)

	R^1	R^{7a}	R^{7b}	R^{7c}	A
1	H	Me	Me	Me	$-(CH_2)_2-$
2	Me	Me	Me	Me	$-(CH_2)_2-$
3	H	Me	Me	Me	$-(CH_2)_4-$
4	H	Me	Me	Me	$-S(CH_2)_4-$
5	H	Me	Me	Me	$-O(CH_2)_4-$

[0067]
[A table 22]

表２２

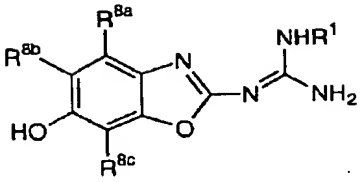


(I－A41)

	R^1	R^{8a}	R^{8b}	R^{8c}
1	H	Me	Me	Me
2	Me	Me	Me	Me
3	H	Me	t－Bu	t－Bu
4	H	Me	Ph	Me
5	H	Me	Bz	Me

[0068]
[A table 23]

表２３

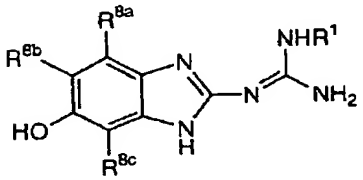


(I－B41)

	R1	R8a	R8b	R8c
1	H	Me	Me	Me
2	Me	Me	Me	Me
3	H	Me	t－Bu	t－Bu
4	H	Me	Ph	Me
5	H	Me	Bz	Me

[0069]
[A table 24]

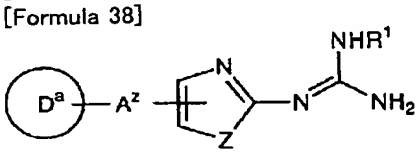
表２４



(I－C41)

	R1	R8a	R8b	R8c
1	H	Me	Me	Me
2	Me	Me	Me	Me
3	H	Me	t－Bu	t－Bu
4	H	Me	Ph	Me
5	H	Me	Bz	Me

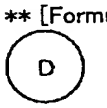
[0070]
[Methods for Producing the Invented Chemical Compound] The inside of this invention compound shown by the general formula (I), (1) general formula (IA)
[Formula 38]



(IA)

[0071] Inside of [type, [Formula 39]

** [Formula 40]



It is although the same semantics is expressed, [Formula 41]

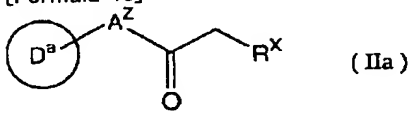
The radical which inner R3 can remove from the alkyl group of C 1–4, the acyl group of C 2–5, or an acid (For example, the alkoxyalkyl group of C 2–4) is expressed, and R6 is the alkyl group of C 1–4, the acyl group of C 2–5, a phenyl group, and phenyl. – Although a radical (for example, alkoxyalkyl group of C 2–4) removable [with C1 – 4 alkyl groups, or an acid] shall be expressed and AZ expresses the same semantics as A, a sulfur atom should mind

alkylene. [Formula 42]

Except for the case where it is alike and has joined together, other marks express the same semantics as the above.] The compound come out of and shown is a general formula (IIa).

[0072]

[Formula 43]

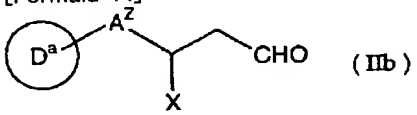


(IIa)

(Among a formula, RX expresses a halogen atom or an acetyloxy radical, and, as for other marks, expresses the same semantics as the above.) Or a general formula (IIb)

[0073]

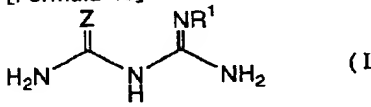
[Formula 44]



(IIb)

(— among a formula, X expresses a halogen atom and other marks express the same semantics as the above.) — the compound shown and general formula (IIIa)

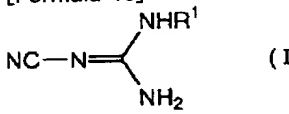
[Formula 45]



(IIIa)

(— all marks express the same semantics as the above.) — the compound shown or general formula (IIIb)

[Formula 46]

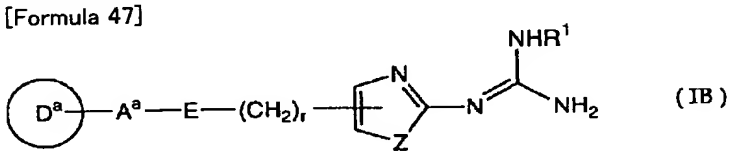


(IIIb)

(— all marks express the same semantics as the above.) — when it is the radical which is made to react with the compound shown or R3 or R6 can remove from an acid, it can manufacture by performing acid treatment succeedingly.

[0074] Moreover, the inside of this invention compound shown by (2) general formulas (I), a general formula (IB)

[Formula 47]

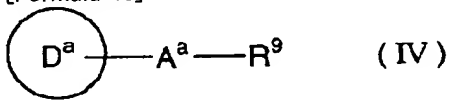


(IB)

[0075] (Aa expresses the alkylene group of C 1–6 among a formula, E expresses a sulfur atom or an oxygen atom, r expresses the integer of 1–6 and other marks express the same semantics as the above.) However, the total number of the carbon atom of Aa and r (CH2) is seven or less. The compound shown is a general formula (IV).

[0076]

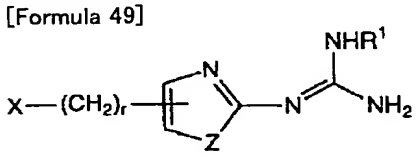
[Formula 48]



(IV)

(— among a formula, R9 expresses a hydroxyl group or an acetyl thio radical, and other marks express the same semantics as the above.) — the compound shown and general formula (V)

[Formula 49]

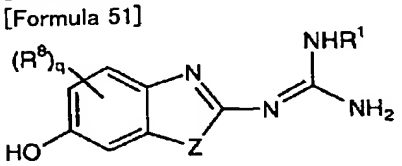


(— all marks express the same semantics as the above among a formula.) — or [making it react with the compound shown] — or [Formula 50]

When inner R3 or R6 are a radical removable [with an acid], it can manufacture by performing acid treatment succeedingly.

[0077] Moreover, the inside of this invention compound shown by (3) general formulas (I), a general formula (IC)

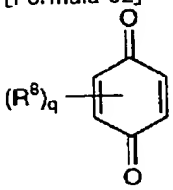
[Formula 51]



(IC)

(— all marks express the same semantics as the above among a formula.) — the compound shown — general formula (VI)

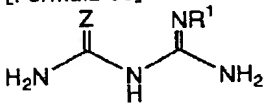
[Formula 52]



(VI)

(— all marks express the same semantics as the above among a formula.) — the compound shown and general formula (IIIa)

[Formula 53]



(IIIa)

(— all marks express the same semantics as the above.) — it can manufacture by making it react with the compound shown.

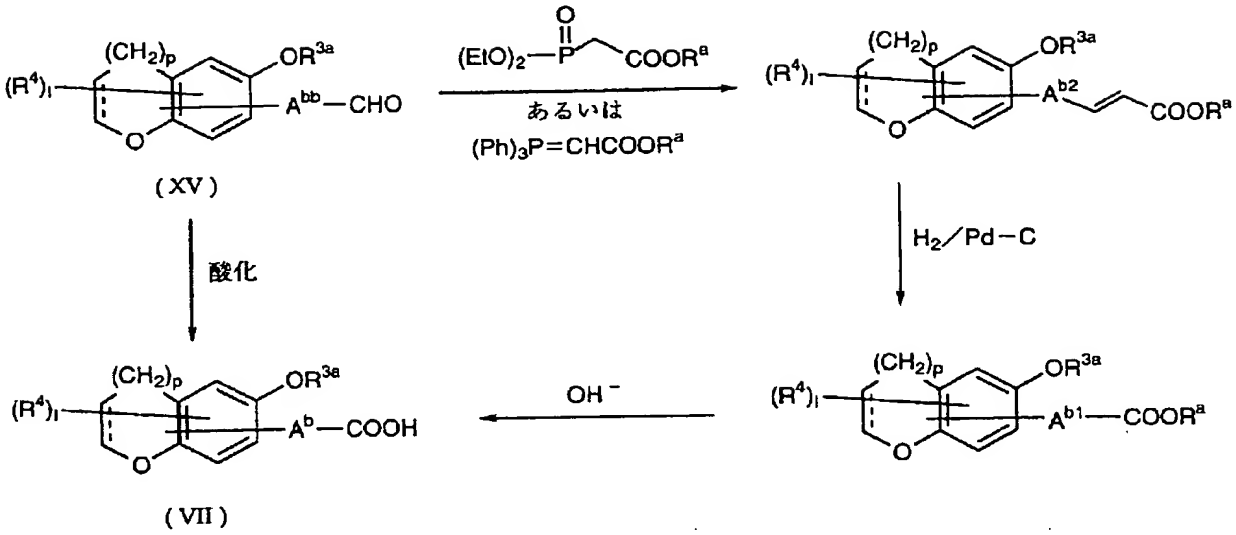
[0078] a general formula (IIa) — with or (IIb), the reaction with a general formula (IIIa) is well-known, for example, is performed among an alcoholic solvent (a methanol, ethanol, etc.) by making it react at the temperature of 80-120 degrees C. a general formula (IIa) — with or (IIb), the reaction with a general formula (IIIb) is well-known, for example, is performed by making it react at 10-40 degrees C among an alcoholic solvent (a methanol, ethanol, etc.) and under acids (hydrochloric acid etc.) existence. Processing by the acid is performed by making it react under the inside of an alcoholic solvent, organic acids (an acetic acid, trifluoroacetic acid, etc.), or inorganic-acids (hydrochloric-acid, sulfuric acid, etc.) existence (a methanol, ethanol, etc.). The reaction of a general formula (IV) and a general formula (V) is well-known, for example, is performed by making it react under base (sodium ethoxide etc.) existence among an alcoholic solvent (a methanol, ethanol, etc.). The reaction of a general formula (VI) and a general formula (IIIa) is well-known, for example, is performed by making it react under acids (hydrochloric acid etc.) existence among an alcoholic solvent (a methanol, ethanol, etc.).

[0079] The general formula (IIa) used as a start raw material and (IIb) the compound shown by (IV) can be manufactured by the method shown in the reaction production process types 1-8, or the well-known method, for example, a method given [this] in a specification.

[0080]

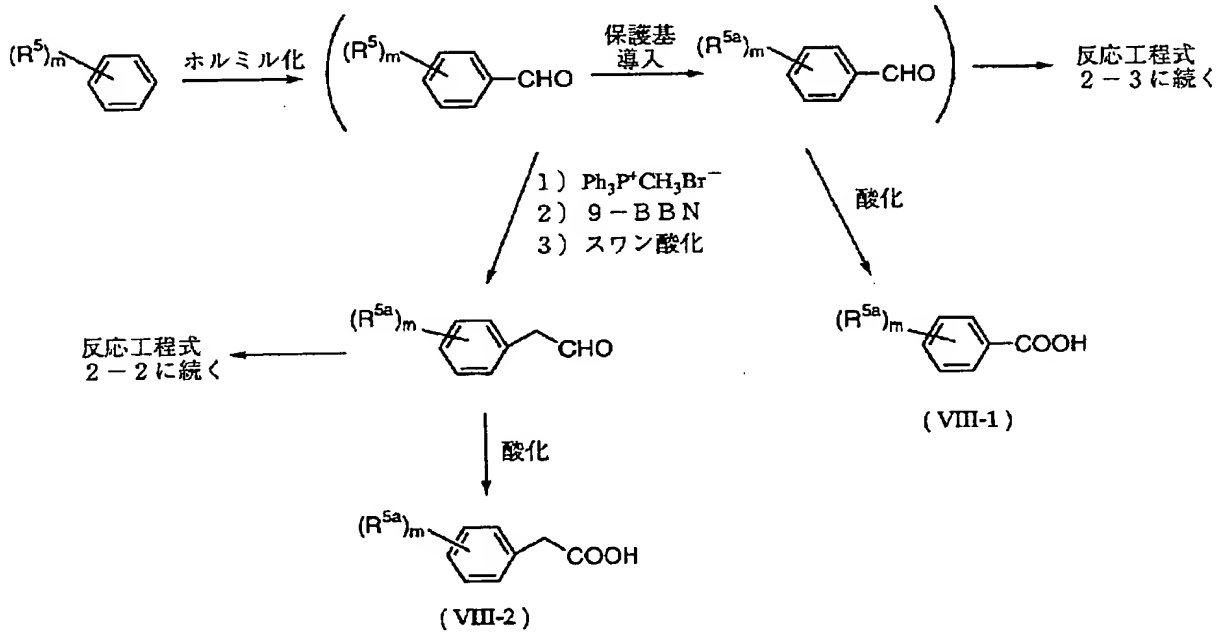
[Formula 54]

反応工程式１



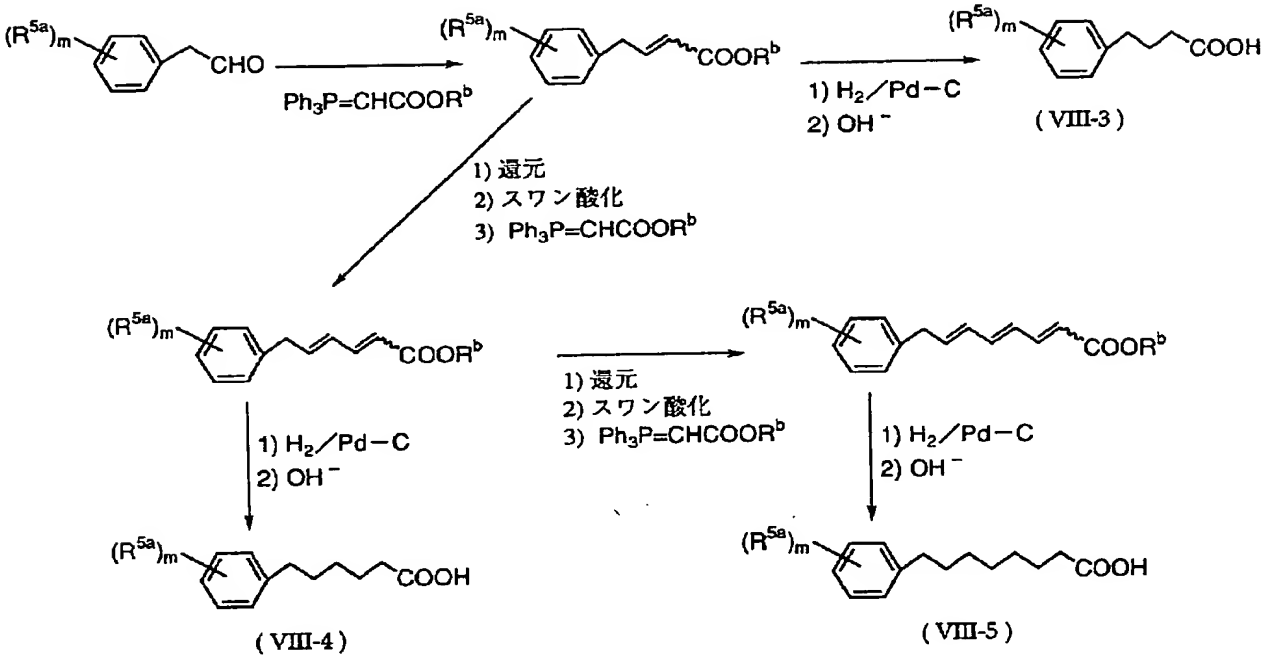
[0081]
[Formula 55]

反応工程式２－１



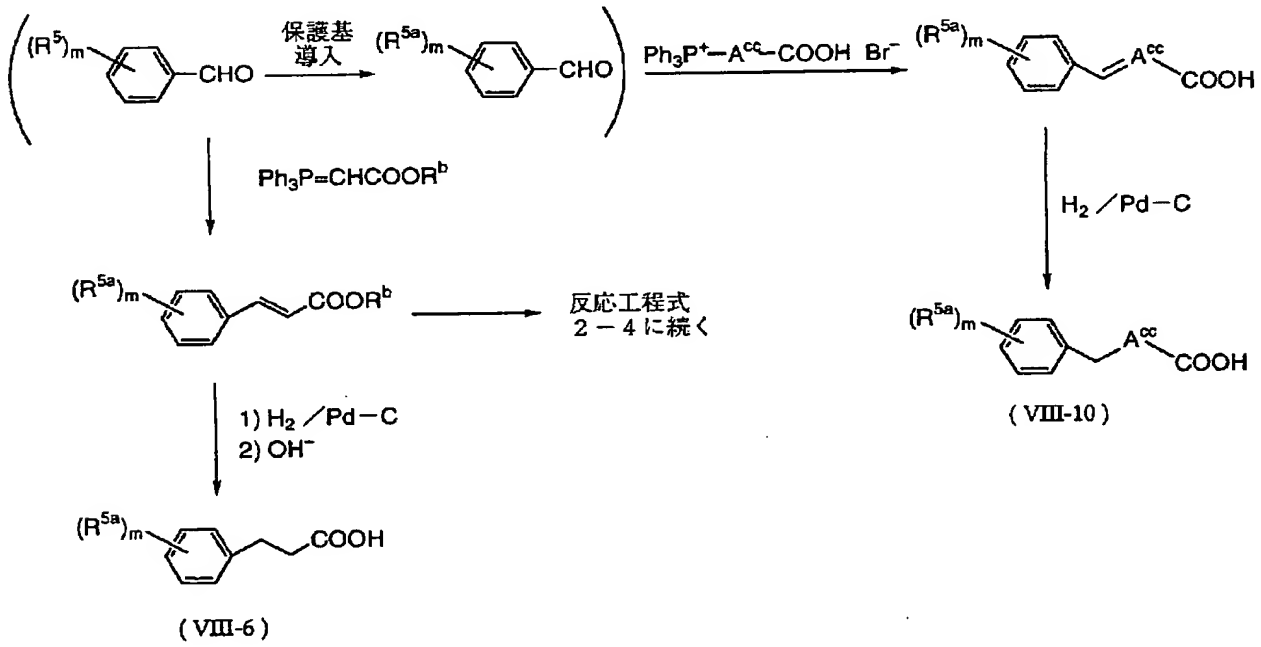
[0082]
[Formula 56]

反応工程式２－２



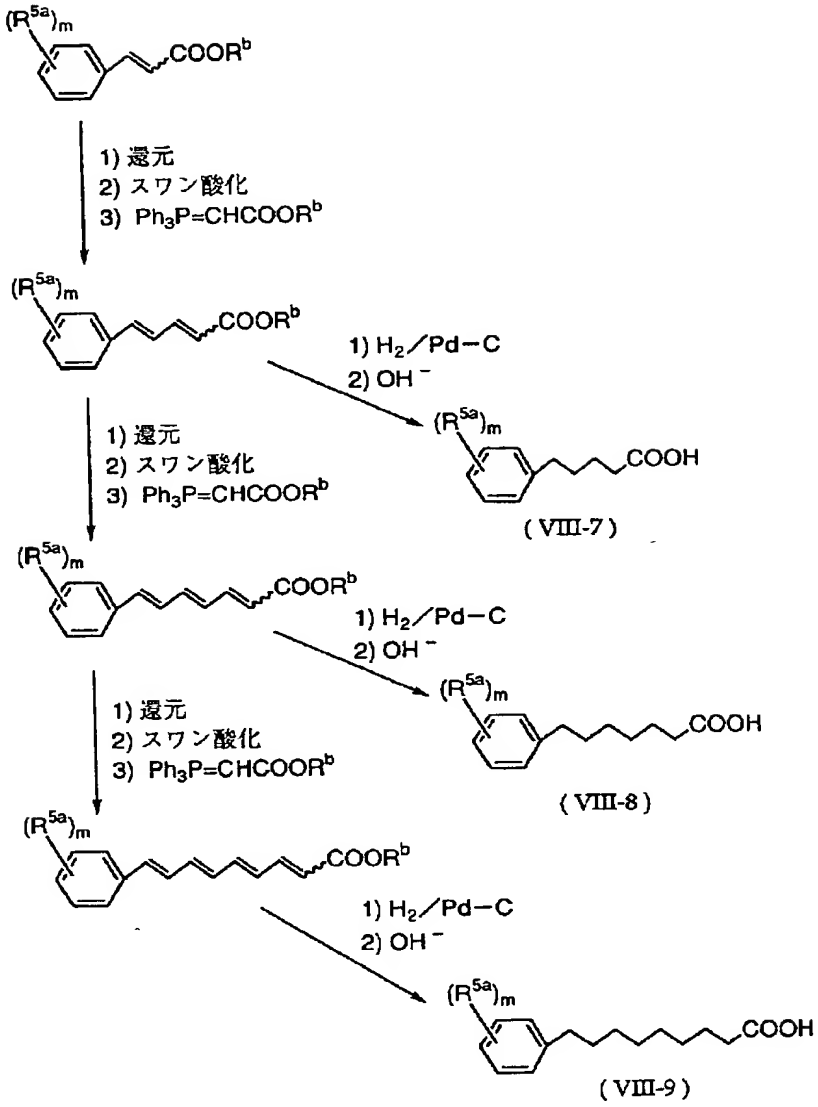
[0083]
[Formula 57]

反応工程式２－３



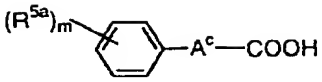
[0084]
[Formula 58]

反応工程式２－４

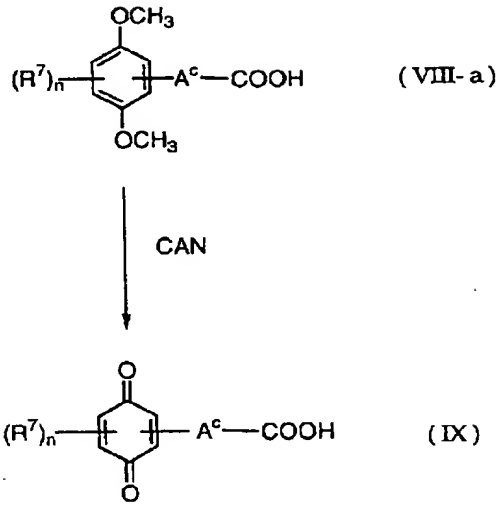


[0085]
[Formula 59]

反応工程式 3



(VIII) = (VIII-1~10)

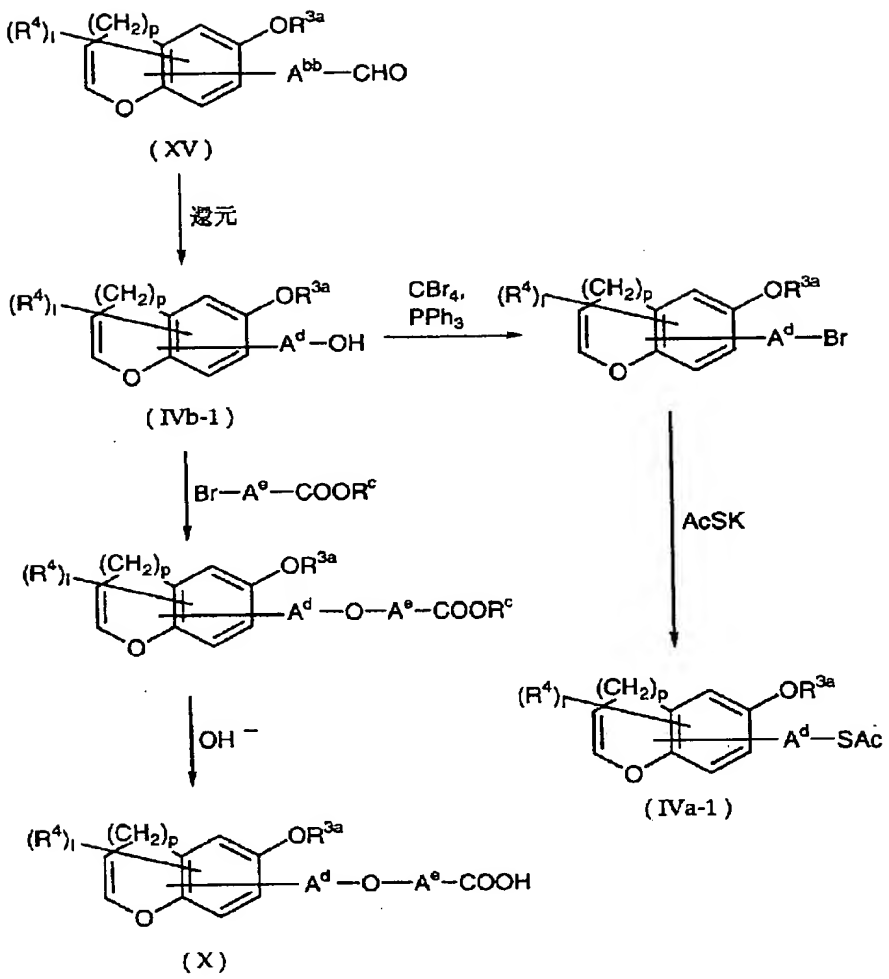


(VIII- a)

(IX)

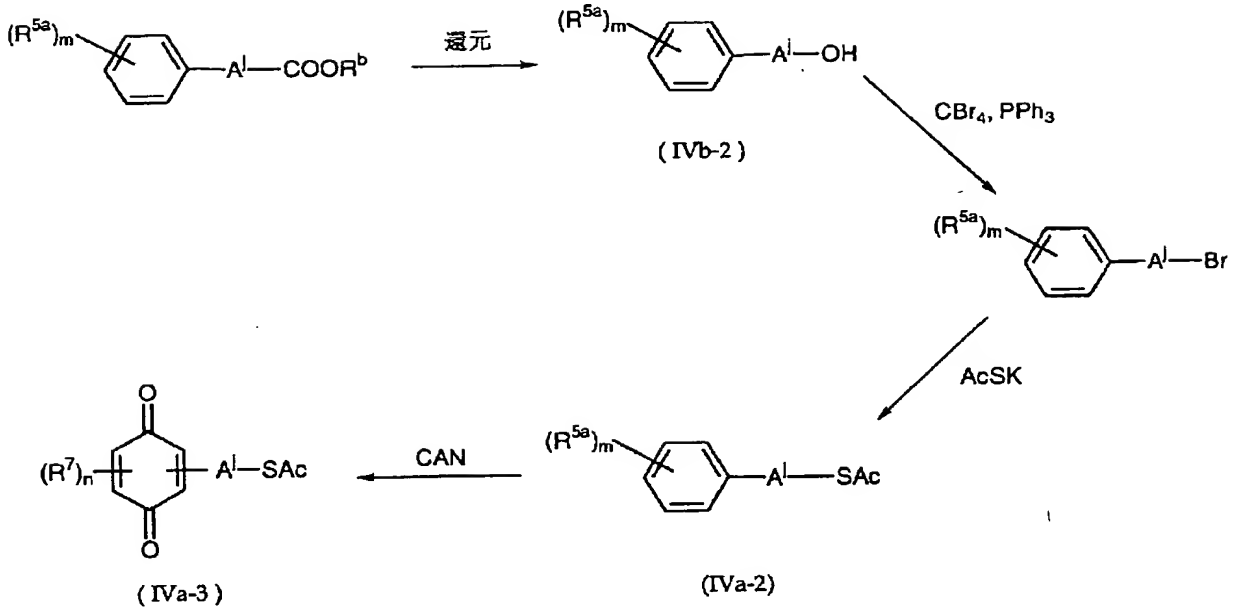
[0086]
[Formula 60]

反応工程式4



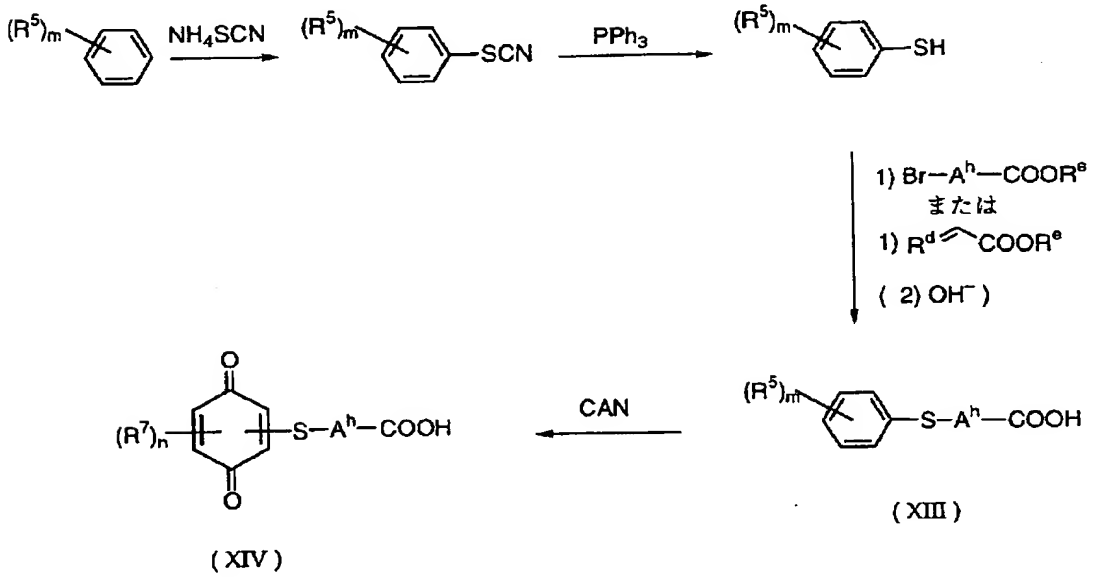
[0087]
[Formula 61]

反応工程式5



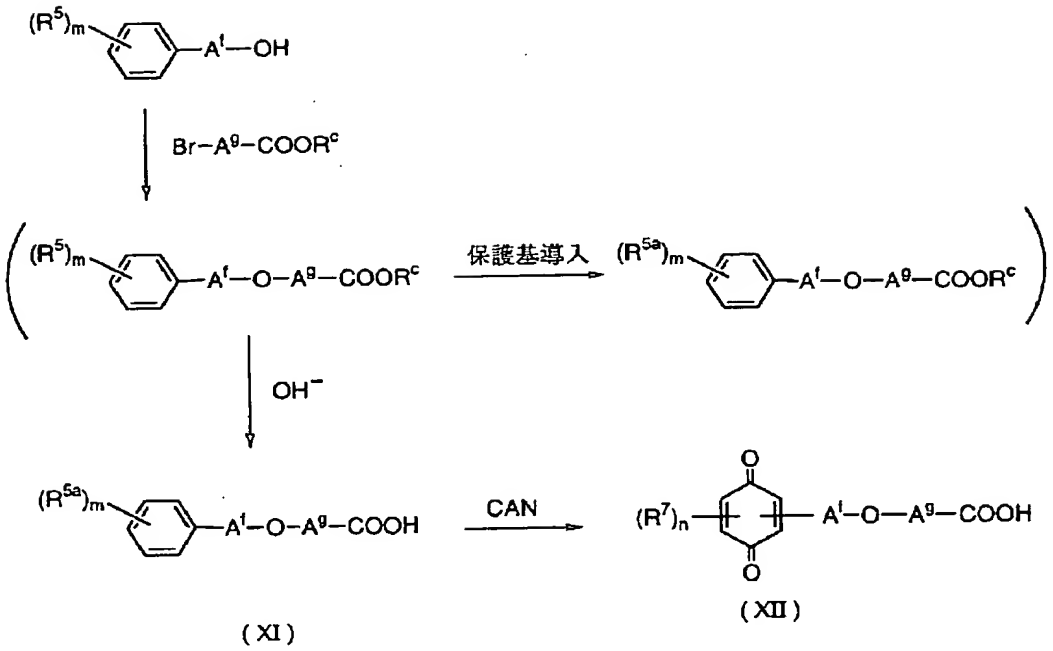
[0088]
[Formula 62]

反応工程式6



[0089]
[Formula 63]

反応工程式 7

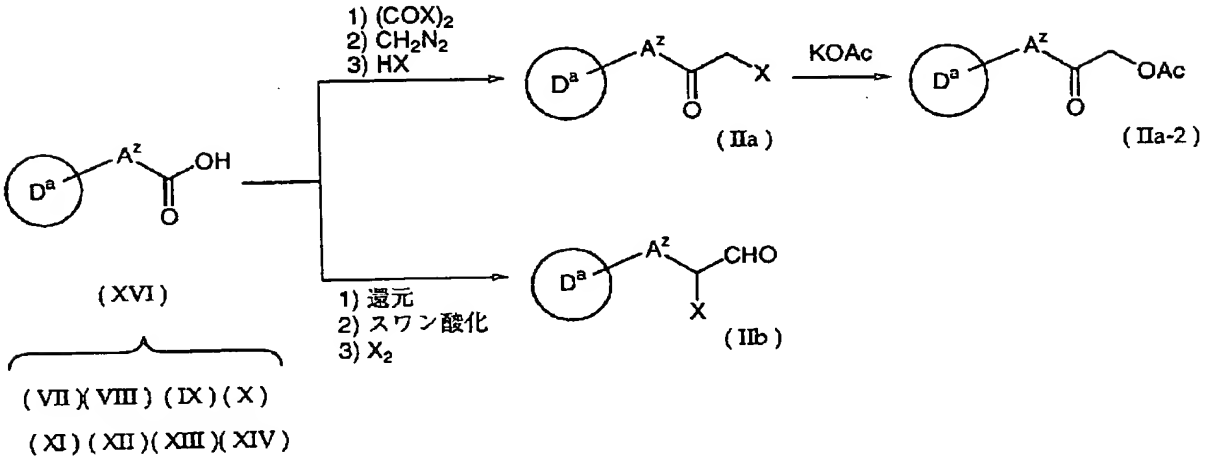


(XI)

(XII)

[0090]
[Formula 64]

反応工程式 8

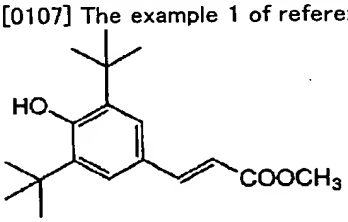


(VII)(VIII) (IX) (X)
(XI) (XII) (XIII) (XIV)

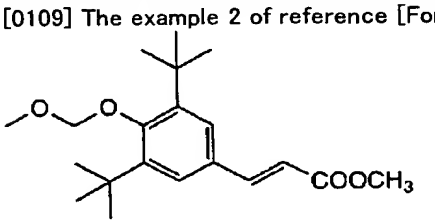
[0091] Ab expresses the alkylene group of single bond or C 1-8 among a reaction production process type, and Ab1 is, The alkylene group of C 7 or 8 is expressed. Ab2 The alkylene group of C 5 or 6 is expressed. Abb The alkylene group of single bond or C 1-6 is expressed. Ac The alkylene group of single bond or C 1-8 is expressed. Ac1 By expressing the alkylene group of C 1-7, Ac2 expresses the alkylene group of C 2-8, Ad expresses the alkylene group of C 1-6, and Ae is the alkylene group (however, the total number of the carbon of Ad and Ae is seven or less.) of C 1-6. It expresses and Af expresses the alkylene group of single bond or C 1-6. Ag The alkylene group of C 1-7 (however, the total number of the carbon of Af and Ag is seven or less.) It expresses, Ah expresses the alkylene group of C 1-7, Ai expresses the alkylene group of C 1-6, and Aj expresses the alkenylene group of C 2-8, [0092] R3a is a radical removable [with the alkyl group of C 1-4, the acyl group of C 2-5, or an acid]. (For example, the alkoxyalkyl group of C 2-4) is expressed. R5a The alkyl group of C 1-7, OR6a set (inside of radical and R6a is the alkyl group of C 1-4, the acyl group of C 2-5, a radical (for example, alkoxyalkyl group of C 2-4) removable [with an acid], a phenyl group, or phenyl - C1 - 4 alkyl groups are expressed.) A halogen atom, a phenyl group, or phenyl - C1 - 4 alkyl groups are expressed. Rb The alkyl group of C 1-4 is expressed, and Rc expresses the alkyl group of C 1-4. Rd A hydrogen atom or the alkyl group of C 1-5 is expressed. Re A hydrogen atom or the alkyl group of C 1-4 is

expressed. Ph a phenyl group — expressing — Et — an ethyl group — expressing — AcSK — a thioacetic-acid potassium — expressing — CAN — a cerium ammonium nit rate — expressing — 9-BBN — 9- a bora — bicyclo [3.3.1] nonane is expressed.
[0093] The other starting material and each other reagent in this invention are well-known in itself, or can be manufactured by the well-known method. For example, the manufacture method of the compound shown by the general formula (V) is indicated by the JP,53-147069,A specification. Moreover, the compound shown by the general formula (XV) is indicated by the PCT application number JP 95/No. 294 specification.
[0094] A resultant can be refined by methods, such as high performance chromatography using the distillation under the usual purification means, for example, ordinary pressure, or reduced pressure, silica gel, or a magnesium silicate, thin-layer chromatography, a column chromatography or washing, and recrystallization. Purification may be performed for every reaction and you may carry out after some reaction termination.
[0095]
[Effect of the Invention] The Maillard reaction inhibitory action of this invention compound was checked by the screening system using various protein and various sugar. For example, it was checked by the screening system described below.
(1) After having dissolved the experiment method lysozyme and the fructose in the 0.2M sodium phosphate buffer solution (pH 7.4) so that it might become the concentration of 10mg [ml] /and 100mM, respectively, and carrying out an incubation for three days at 37 degrees C, electrophoresis was performed for the constant rate using ejection SDS-PAGE. The quantum of the amount of generation of a dimer was carried out with the densitometer after dyeing by Coomassie Brilliant Blue (Coomassie Brilliant Blue) R-250 0.2% after electrophoresis. It added before the incubation, and this invention compound investigated the depressor effect over the dimer generation in various concentration, and calculated IC50 value.
(2) A result is shown in a table 25.
[0096]
[A table 25]
Example number IC50(muM) 1 4.4 1 (1) 2.9 1 (5) 9.2 1 (30) 4.4 1 (37) 1.5 1 (40) 2.7 1 (44) 5.5 [0097] The antioxidation operation of this invention compound was checked by the screening system which investigates the peroxylipid generation depressor effect described below.
(1) Maleness made to abstain from food overnight [experiment method] Sprague Dawley Perfusion was carried out from the portal vein in 0.9% sodium chloride aqueous solution which ice-cooled the rat under anesthesia, and the liver organization was extracted. It considered as the homogenate 10% using 1.15% potassium chloride aqueous solution which ice-cooled the extraction liver. FeCl2 200mM was added to obtained homogenate 200microl, and it incubated at 37 degrees C for 1 hour. OOKAWA's and others (Ohkawa) method [Analytical Biochemistry, 95, and 351 reference (1979)] — following — the amount of generation of peroxylipid — thiobarbituric acid (TBA) — it measured by law. It added before the incubation, and this invention compound investigated the effect, and computed IC50 value.
(2) A result is shown in a table 26.
[0098]
[A table 26]
Example number IC50(muM) 1 3.8 1 (5) 3.7 1 (29) 2.9 1 (32) 1.8 1 (39) 0.82 1 (25) 16 1 (47) 0.56 1 (41) 0.45 3 0.96
[0099] A table 25 and a table 26 show that this invention compound, its nontoxic salt, and its acid addition salt have Maillard reaction inhibitory action and an antioxidation operation.
[0100]
[Toxicity] The toxicity of this invention compound was low enough, and it was checked that it can be enough used for safety as drugs.
[0101]
[Application in drugs] Since this invention compounds shown by the general formula (I) and those acid addition salts check a Maillard reaction, they are useful to the therapy and/or prevention of various diabetic complications, for example, a coronary artery nature heart disease, peripheral circulatory bisturdance, the cerebrovascular disease, the diabetes-mellitus sexual nerosis, a nephropathy, arteriosclerosis, the arthrosclerosis, a cataract, a retinopathy and the disease caused by aging, for example, atherosclerosis, senile cataract, and cancer. Moreover, since this invention compounds shown by the general formula (I) and those acid addition salts have an antioxidation operation, i.e., the operation which controls the reaction of a free radical, its peroxylipid production is useful to the therapy and/or prevention of the various diseases used as a cause, for example, arteriosclerosis, diabetes mellitus, myocardial infarction, peripheral circulatory bisturdance, the cerebrovascular disease, cancer, inflammation, a digestive system disease, and aging.
[0102] In order to use this invention compounds shown by the general formula (I), and those acid addition salts for the above-mentioned purpose, a medicine is prescribed for the patient by taking orally or parenteral usually systemic or locally. Although a dose changes with age, weight, a symptom, a curative effect, a medication method, processing times, etc., it is usually administered orally several times from 1 time per day in 1mg - 1000mg per time per one adult, or parenteral administration (it administers intravenously preferably) is carried out several times from 1 time per day in 0.1 mg-100mg per time per one adult. As described above, of course, since a dose is changed on condition that versatility, an amount smaller than the above-mentioned dose range may be enough as it, and it may be required

across a range.
[0103] In case this invention compound is prescribed for the patient, the injections for the solid-state constituent for internal use, a liquid constituent and other constituents, and parenteral administration, external preparations, suppositories, etc. are used.
[0104] A tablet, a pill, a capsule, powder, a granule, etc. are contained in the solid-state constituent for internal use. A hard capsule and a software capsule are contained in a capsule. In such a solid-state constituent, one or the active substance beyond it is mixed with at least one inactive diluent, for example, hydroxypropylcellulose, a microcrystal cellulose, starch, a polyvinyl pyrrolidone, and magnesium aluminometasilicate. The constituent may contain a solubilizing agent like additives other than an inactive diluent, for example, lubricant like magnesium stearate, disintegrator like a calcium carboxymethyl cellulose, glutamic acid, or an aspartic acid according to a conventional method. The coat of a tablet or the pill may be carried out as occasion demands with the film of stomach solubility, such as white soft sugar, gelatin, hydroxypropylcellulose, and hydroxypropylmethylcellulose phthalate, or enteric material, and it may carry out a coat in two or more layers. The capsule of material still like gelatin in which it is absorbed and deals is also included. The liquid constituent for internal use may contain the inactive diluent (for example, purified water, ethanol) generally used including the opacifier permitted in drugs, a solution agent, suspension, syrups, elixirs, etc. This constituent may contain a wetting agent, an adjuvant like suspension, a sweetening agent, a flavor agent, an aromatic, and antiseptics in addition to an inactive diluent. As a constituent of others for internal use, the spray prescribed by the well-known method in itself is contained including one or the active substance beyond it. This constituent may contain a stabilizer like a sodium hydrogensulfite and a buffer which gives isosmotic, for example, a sodium chloride, a sodium citrate, or a citric acid in addition to an inactive diluent. the manufacture method of spray — for example, U.S. Pat. No. 2868691 — and — said — the 3095355th It is indicated in detail by the number specification.
[0105] As injections for the parenteral administration by this invention, the sterile solution agent of aquosity or nonaqueous nature, suspension, and an opacifier are included. As a water solution agent and suspension, distilled water for injection and a physiological saline are contained, for example. As the solution agent of nonaqueous solubility, and suspension, there are propylene glycol, a polyethylene glycol, vegetable oil like olive oil, alcohols like ethanol, polysorbate 80, etc., for example. Such a constituent may also contain an adjuvant still like antiseptics, a wetting agent, an emulsifier, a dispersant, a stabilizing agent, and a solubilizing agent (for example, glutamic acid, an aspartic acid). These are sanitized by the combination or the exposure of filtration and a germicide which lets for example, a bacteria hold filter pass. These manufacture a sterile solid-state constituent again, and they can also use it for sterile water or the sterile solvent for injection before use, dissolving. As a constituent of others for parenteral administration, the pessary for the suppositories for the liquids for external use prescribed by the conventional method, paint like ointment, and intrarectal administration and the administration in a vagina etc. is contained including one or the active substance beyond it.
[0106]
[Related Example(s) and Working Example(s)] Hereafter, although this invention is explained in full detail according to the example of reference, and an example, this invention is not limited to these. The solvent in the parenthesis indicated in the part of separation by the chromatography shows the used expansion solvent, and a rate expresses a volume ratio. Moreover, the inside of the parenthesis indicated in the part of NMR shows the measurement solvent.
[0107] The example 1 of reference [Formula 65]



[0108] Under the argon, it flowed back for 1 hour and the benzene solution (50ml) of a 3 and 5-G t-butyl-4-hydroxy benzaldehyde (11.7g) and triphenyl phospho RIDEN acetic-acid methyl ester (18.4g) was condensed. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:10 ->5:1), and the title compound (14.1g) which has the following physical-properties value was obtained.
TLC:Rf 0.51 (ethyl acetate: n-hexane =1:5).
[0109] The example 2 of reference [Formula 66]

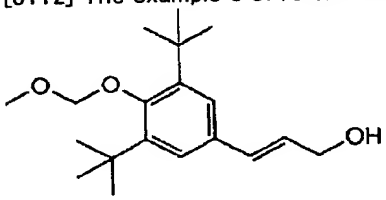


[0110] The DMF solution (20ml) of the compound (8.0g) manufactured in the example 1 of reference under -78 degrees C and an argon was added to the dimethylformamide (DMF) suspension of sodium hydride (60% content;

1.65g). Mixture was agitated for 15 minutes at 0 degree C. Methoxymethyl chloride (2.5ml) was added to the reaction mixture at 0 degree C, and it agitated for 10 minutes, and agitated at the room temperature further for 2 hours. Furthermore, sodium hydride (60% content; 0.83g) and methoxymethyl chloride (1.2ml) were added, and it agitated at the room temperature for 1 hour. Water was added to the reaction solution and ethyl acetate extracted. The organic layer was washed with water and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (8.80g) which has the following physical-properties value was obtained.

[0111] TLC:Rf 0.40 (ethyl acetate: n-hexane =1:9) and NMR(CDCl3):delta 7.65 (1H, d), 7.44 (2H, s), 6.34 (1H, d), 4.91 (2H, s), 3.80 (3H, s), 3.65 (3H, s), 1.45 (18H, s).

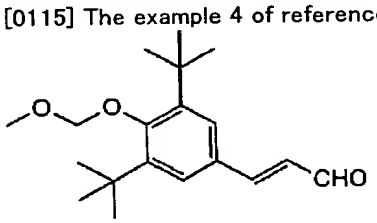
[0112] The example 3 of reference [Formula 67]



[0113] The toluene solution (65.7ml) of a 1M diisobutyl aluminum hydride was added to the methylene chloride solution (30ml) of the compound (8.79g) manufactured in the example 2 of reference under -78 degrees C and an argon. The mixed solution was agitated for 30 minutes at -78 degrees C. Water was added to the reaction solution, 1-N hydrochloric acid neutralized, and ethyl acetate extracted, after making it acidity by the citric acid. Sequential washing of the organic layer was carried out with saturation brine, a saturation sodium hydrogencarbonate, and saturation brine, and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:6), and the title compound (8.03g) which has the following physical-properties value was obtained.

[0114] TLC:Rf 0.11 (ethyl acetate: n-hexane =1:9) and NMR(CDCl3):delta 7.30 (2H, s), 6.57 (1H, d), 6.27 (1H, dt), 4.89 (2H, s), 4.30 (2H, s), 3.64 (3H, s), 1.45 (18H, s).

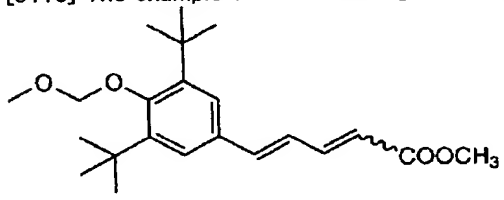
[0115] The example 4 of reference [Formula 68]



[0116] Triethylamine (30ml), dimethyl sulfoxide (DMSO) (25ml), and a SURUFA trioxide pyridine complex (16.6g) were added to the methylene chloride solution (25ml) of the compound (8.0g) manufactured in the example 3 of reference under 0 degree C and an argon. After agitating mixture for 5 minutes at 0 degree C, it agitated for 30 minutes at the room temperature further. It is ****** to the mixed solution of ethyl acetate and water about a reaction solution. Sequential washing of the organic layer was carried out with saturation brine, a citric acid, saturation brine, a saturation sodium hydrogencarbonate, and saturation brine, with magnesium sulfate, after desiccation, it condensed and the title compound which has the following physical-properties value was obtained.

[0117] TLC:Rf 0.80 (ethyl acetate: n-hexane =1:4) and NMR(CDCl3):delta 9.68 (1H, d), 7.49 (2H, s), 7.45 (1H, d), 6.65 (1H, d), 4.93 (2H, s), 3.66 (3H, s), 1.46 (18H, s).

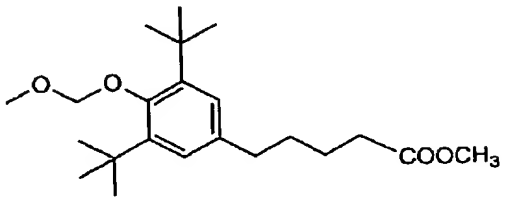
[0118] The example 5 of reference [Formula 69]



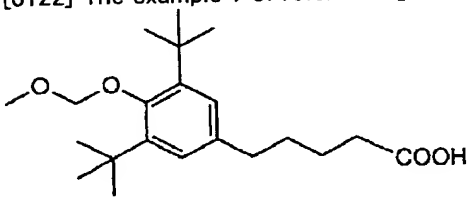
[0119] Under the argon, it flowed back for 13 hours and the compound and the benzene solution (50ml) of triphenyl phospho RIDEN acetic-acid methyl ester (17.52g) which were manufactured in the example 4 of reference were condensed. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (8.05g) which has the following physical-properties value was obtained.

TLC:Rf 0.40 (ethyl acetate: n-hexane =1:10).

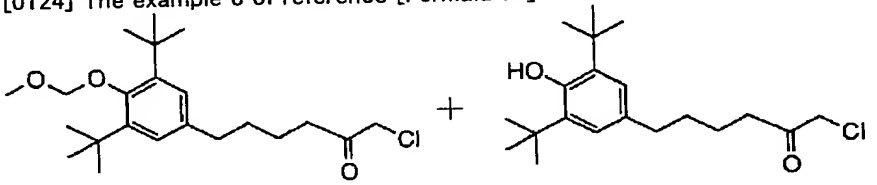
[0120] The example 6 of reference [Formula 70]



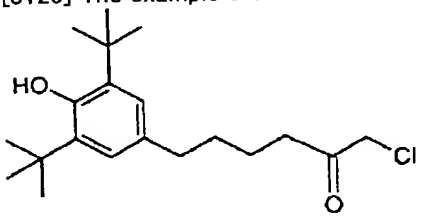
[0121] The methanol solution (20ml) of the compound (8.04g) manufactured in the example 5 of reference and palladium carbon (800mg) was agitated at the room temperature under hydrogen gas for 16 hours. Cerite filtration was carried out and the reaction solution was condensed. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (7.30g) which has the following physical-properties value was obtained.
TLC:Rf 0.37 (ethyl acetate: n-hexane =1:10).
[0122] The example 7 of reference [Formula 71]



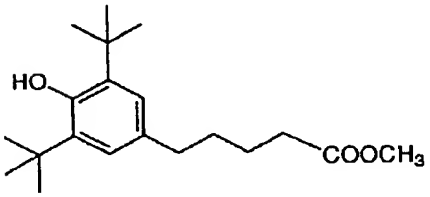
[0123] 2-N sodium hydroxide (35ml) was added to the methanol solution (10ml) of the compound (3.65g) manufactured in the example 6 of reference at 0 degree C. At the room temperature, the mixed solution was agitated for 6 hours and condensed. It acidified with 1-N hydrochloric acid, and ethyl acetate extracted the residue. Saturation brine washed the organic layer, with magnesium sulfate, after desiccation, it condensed and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.07 (ethyl acetate: n-hexane =1:10).
[0124] The example 8 of reference [Formula 72]



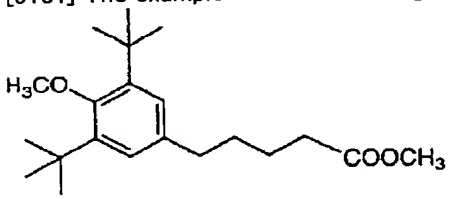
[0125] Oxalyl chloride (1.05ml) and DMF (three drops) were added to the benzene solution (10ml) of the compound manufactured in the example 7 of reference under 0 degree C and an argon. The mixed solution was agitated at the room temperature for 1 hour. The reaction solution was condensed and the residue was dissolved in diethylether. At 0 degree C, it was dropped at it until gas stopped having generated the ethanol solution of diazomethane in the solution, and it was dropped until gas stopped having generated the 1,4-dioxane (10ml) solution of 4 moreN hydrochloric acid at 0 degree C. The solution was diluted with ethyl acetate, saturation brine washed, and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the mixed compound (3.54g) of a title was obtained.
[0126] The example 9 of reference [Formula 73]



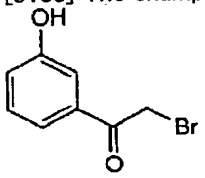
[0127] Since the compound manufactured in the example 8 of reference was mixture with the object which is not used as the object from which the hydroxyl group is protected, it added the 1,4-dioxane solution (10ml) of 4-N hydrochloric acid to the 1,4-dioxane (10ml) of the mixture, and the mixed solution of water (0.5ml) at 0 degree C. The mixed solution was agitated at the room temperature for 12 hours. The reaction solution was condensed and ethyl acetate extracted. Saturation brine washed the organic layer and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (3.18g) which has the following physical-properties value was obtained.
[0128] TLC:Rf 0.42 (ethyl acetate: n-hexane =1:10) and NMR(CDCl3):delta 6.96 (2H, s), 5.03 (1H, s), 4.05 (2H, s), 2.62 (2H, t), 2.54 (1H, t), 1.50-1.80 (4H, m), 1.43 (18H, s).
[0129] The example 10 of reference [Formula 74]



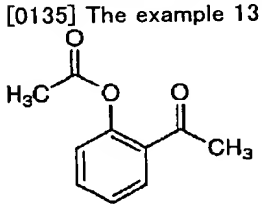
[0130] Using the compound (3.65g) manufactured in the example 6 of reference, it was operated like the example 9 of reference, and the title compound (3.58g) which has the following physical-properties value was obtained.
TLC:Rf 0.41 (ethyl acetate: n-hexane =1:10) and NMR(CDCl3):delta 6.96 (2H, s), 5.03 (1H, s), 3.67 (3H, s), 2.53 (2H, t), 2.35 (1H, t), 1.50-1.80 (4H, m), 1.43 (18H, s).
[0131] The example 11 of reference [Formula 75]



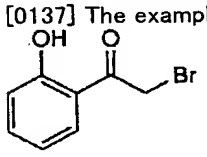
[0132] Sodium hydride (60% content; 1.20g) was added to the DMF solution (25ml) of the compound (3.20g) manufactured in the example 10 of reference. Suspension was agitated for 30 minutes at 0 degree C. Iodation methane (2.49ml) was added to the reaction mixture at 0 degree C. Mixture was agitated at the room temperature for 24 hours. Saturated ammonium chloride was added to the reaction mixture, and ethyl acetate extracted. Saturated ammonium chloride and saturation brine washed the organic layer, and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (3.30g) which has the following physical-properties value was obtained.
TLC:Rf 0.38 (ethyl acetate: n-hexane =1:10).
[0133] The example 12 of reference [Formula 76]



[0134] The bromine (378microl) was slowly added to the acetic acid of a 3'-hydroxy acetophenone (1.0g), and the mixed solution (3.0ml+0.5ml) of a tetrahydro furan (THF). Mixture was agitated at the room temperature for 1.5 hours. The reaction solution was diluted with ethyl acetate, sequential washing was carried out with a saturation sodium hydrogencarbonate, water, and saturation brine, and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:5), and the title compound (1.10g) which has the following physical-properties value was obtained.
TLC:Rf 0.32 (ethyl acetate: n-hexane =1:3).
[0135] The example 13 of reference [Formula 77]

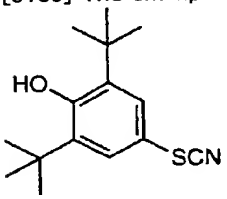


[0136] A pyridine (1.5ml), an acetic anhydride (1.5ml), and 4-dimethylaminopyridine (0.03g) were added to the methylene chloride solution (10ml) of a 2'-hydroxy acetophenone (1.5g). At the room temperature, the mixed solution was agitated for 3 hours and condensed. The residue was diluted with ethyl acetate, sequential washing was carried out with water, 1-N hydrochloric acid, and saturation brine, with magnesium sulfate, after desiccation, it condensed and the title compound (2.8g) which has the following physical-properties value was obtained.
TLC:Rf 0.15 (ethyl acetate: n-hexane =1:10).
[0137] The example 14 of reference [Formula 78]

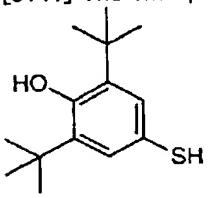


[0138] The pyridinium star's picture par star's picture (1.58g) was added to the THF solution (10ml) of the compound

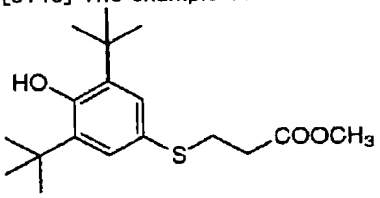
(800mg) manufactured in the example 13 of reference. Mixture was agitated at the room temperature for 1 hour. The reaction solution was diluted with ethyl acetate, and it washed with water, and condensed after desiccation with magnesium sulfate. After leaving the residue overnight, it refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (593mg) which has the following physical-properties value was obtained.
TLC:Rf 0.30 (ethyl acetate: n-hexane =1:3).
[0139] The example 15 of reference [Formula 79]



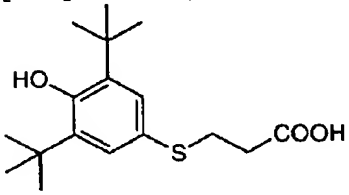
[0140] After pouring chlorine gas into the methanol solution (25ml) of 2 and 6-G t-butylphenol (5.0g) and ammonium thiocyanate (3.9g) at 0 degree C for 20 minutes, argon substitute was carried out, and ammonia gas was poured in at 0 degree C for 20 minutes, and was agitated for 30 more minutes. The reaction solution was poured out into iced water and precipitate was ****(ed) after neglect overnight. The sediment was refined by column chromatography (ethyl acetate: n-hexane =1:15), and the title compound (5.2g) which has the following physical-properties value was obtained.
TLC:Rf 0.38 (ethyl acetate: n-hexane =1:15).
[0141] The example 16 of reference [Formula 80]



[0142] After adding triphenyl phosphine (4.8g) and water (0.66ml) to the acetone solution (20ml) of the compound (4.8g) manufactured in the example 15 of reference at 0 degree C, it agitated at the room temperature for 3 hours. The reaction solution was condensed, the residue was refined by column chromatography (ethyl acetate: n-hexane =1:30), and the title compound (3.0g) which has the following physical-properties value was obtained.
TLC:Rf 0.58 (ethyl acetate: n-hexane =1:5).
[0143] The example 17 of reference [Formula 81]

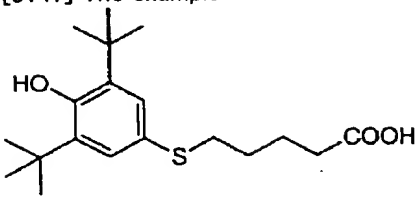


[0144] Triethylamine (82microl) and a methyl acrylate (927microl) were added to the methanol solution (5ml) of the compound (817mg) manufactured in the example 16 of reference, and it agitated for 20 minutes at the room temperature. The reaction solution was condensed, the residue was refined by column chromatography (ethyl acetate: n-hexane =1:20), and the title compound (817mg) which has the following physical-properties value was obtained.
TLC:Rf 0.15 (ethyl acetate: n-hexane =1:20).
[0145] The example 18 of reference [Formula 82]



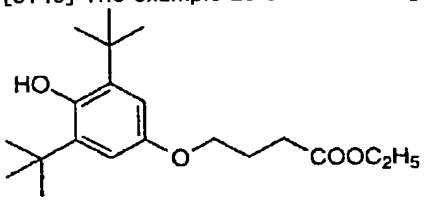
[0146] The lithium-hydroxide (528mg) aqueous solution was added to the methanol solution (5ml) of the compound (815mg) manufactured in the example 17 of reference, and it agitated at the room temperature for 1 hour. The reaction solution was condensed. In addition, ethyl acetate extracted 1-N hydrochloric-acid aqueous solution to it until pH became the residue 1. Water and saturation brine washed the organic layer, with magnesium sulfate, after desiccation, it condensed and the title compound (776mg) which has the following physical-properties value was obtained.
TLC:Rf 0.34 (ethyl acetate: n-hexane =1:1)

[0147] The example 19 of reference [Formula 83]



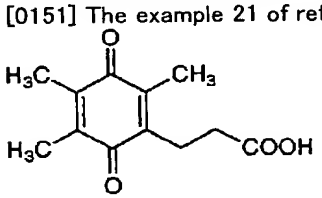
[0148] Diisopropyl ethylamine (667microl) and 5-bromine valeric acid (694mg) were added to the DMF solution (15ml) of the compound (760mg) manufactured in the example 16 of reference, and it agitated at the room temperature overnight. Iced water was added to the reaction solution and ethyl acetate extracted. Water and saturation brine washed the organic layer, and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (chloroform: methanol =20:1), and the title compound (485mg) was obtained.

[0149] The example 20 of reference [Formula 84]



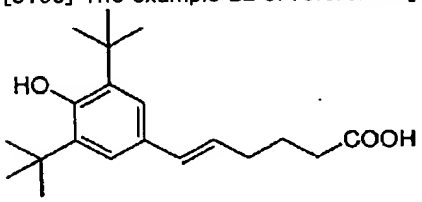
[0150] Sodium hydride (356mg) was added to the DMF solution (15ml) of 2,5-di-tert-butylhydroquinone (1.8g) at 0 degree C, and 30 between was agitated at the room temperature. 4-bromine butyl acid ethyl (1.3ml) was added to the reaction solution at 0 degree C, and it agitated at 60 degrees C overnight. Iced water was added to the reaction solution and ethyl acetate extracted. Water and saturation brine washed the organic layer, and it dried with magnesium sulfate. The solvent was distilled off, the residue was refined by column chromatography (ethyl acetate: n-hexane =1:30), and the title compound (1.73g) which has the following physical-properties value was obtained.
TLC:Rf 0.66 (ethyl acetate: n-hexane =1:3).

[0151] The example 21 of reference [Formula 85]



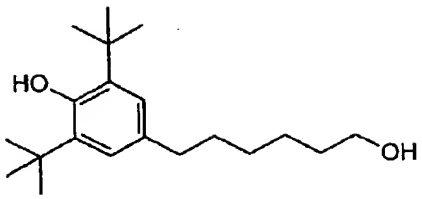
[0152] 3, 6-dimethoxy - Make it be the same as that of the example 7 of example of example of reference 1 -> reference 6 -> reference using a 2, 4, and 5-trimethyl benzaldehyde. In 50% acetonitrile aqueous solution (50ml) of obtained 3-(3, 6-dimethoxy - 2, 4, 5-trimethyl phenyl) propanoic acid (2.07g), 50% acetonitrile aqueous solution (25ml) of a cerium ammonium nit rate (9.92g) was added at 0 degree C, and it agitated for 15 minutes. The reaction solution was filled with the sodium-hydrogencarbonate aqueous solution, and ethyl acetate extracted. Water and saturation brine washed the organic layer, it condensed after desiccation with magnesium sulfate, and the title compound (0.91g) was obtained.

[0153] The example 22 of reference [Formula 86]

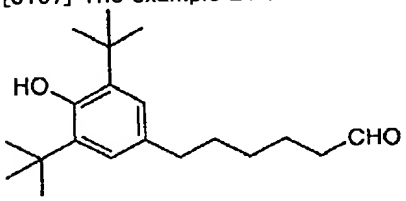


[0154] The DMSO solution (20ml) suspension of sodium hydride (60% content; 865mg) was agitated at 70 degrees C for 1 hour. The DMSO solution (10ml) of 5-(triphenyl phosphine) pentanoic acid star's picture (4.78g) was dropped at 10-20 degrees C, and was agitated for 30 minutes at the room temperature. The DMSO solution (10ml) of a 3 and 5-G t-butyl-4-hydroxy-benzaldehyde (1.00g) was dropped at 10-20 degrees C, and it agitated at the room temperature overnight. Water was filled with the reaction solution, 2-N hydrochloric acid was added, and the JIECHIERU ether extracted. Water and saturation brine washed the organic layer, and it condensed after desiccation with magnesium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:3), and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.15 (ethyl acetate: n-hexane =1:3).

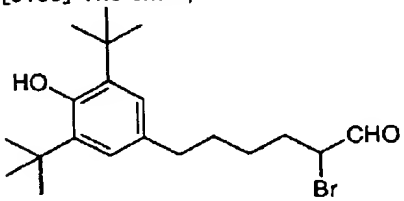
[0155] The example 23 of reference [Formula 87]



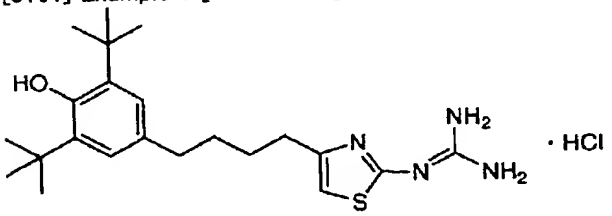
[0156] The lithium aluminum hydride (30mg) was added to the compound and the THF solution (3ml) of a 6-(3, 5-t-butyl-4-hydroxyphenyl)-5-hexene acid (100mg) which operated it like the example 6 of reference, and were obtained at 0 degree C using the compound manufactured in the example 22 of reference, and it agitated at the room temperature for 1 hour. After churning, the saturation sodium-sulfate aqueous solution was dropped at the reaction solution, and it sodium-sulfate-****(ed), and filtered. The filtrate was condensed, the residue was refined by column chromatography (ethyl acetate: n-hexane =1:5 ->1:3), and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.20 (ethyl acetate: n-hexane =1:3).
[0157] The example 24 of reference [Formula 88]



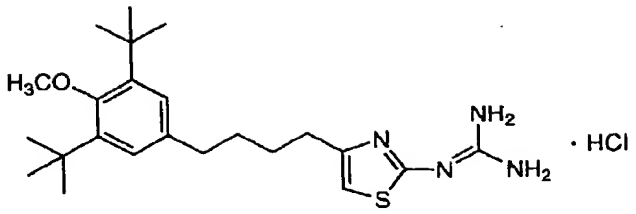
[0158] The methylene chloride solution (1ml) of oxalyl chloride (0.025ml) was cooled at -70 degrees C. The methylene chloride solution (1ml) of DMSO (0.04ml) was dropped there. The mixed solution was agitated for 10 minutes. The methylene chloride solution (1ml) of the compound manufactured in the example 23 of reference was added to the reaction solution, and it agitated for 30 minutes. Triethylamine (0.2ml) was added to the reaction solution, the dry ice bath was removed, and it agitated for 30 minutes. The ether extracted the reaction solution. Water and saturation brine washed the organic layer, with magnesium sulfate, after desiccation, it condensed and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.59 (ethyl acetate: n-hexane =1:3).
[0159] The example 25 of reference [Formula 89]



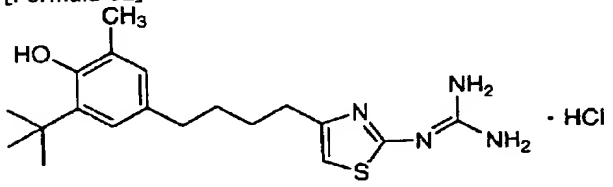
[0160] The chloroform solution (0.25ml) of a bromine (0.07ml) was dropped at the chloroform solution (10ml) of the compound manufactured in the example 24 of reference at -20 degrees C. The mixed solution was returned to the room temperature after 1-hour churning at -20 degrees C. It cooled at -20 degrees C again, the chloroform solution (0.12ml) of a bromine (0.04ml) was dropped, and it agitated for 30 minutes at -20 degrees C. The reaction solution was condensed, the residue was refined by column chromatography (ethyl acetate: n-hexane =1:30), and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.43 (ethyl acetate: n-hexane =1:10).
[0161] Example 1 [Formula 90]



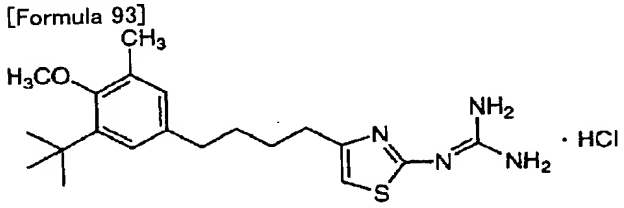
[0162] The compound (2.0g) manufactured in the example 9 of reference and the methanol solution (20ml) of guanidino thiourea (662mg) were flowed back for 12 hours. The reaction solution was condensed, it recrystallized in diethylether, and the title compound (2.42g) which has the following physical-properties value was obtained.
[0163] TLC:Rf 0.34 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 6.96 (2H, s), 6.46 (1H, s), 5.04 (1H, s), 2.67 (2H, t), 2.54 (2H, t), 1.70-1.62 (4H, m), 1.43 (18H, s).
[0164] Example 1 (1)
[Formula 91]



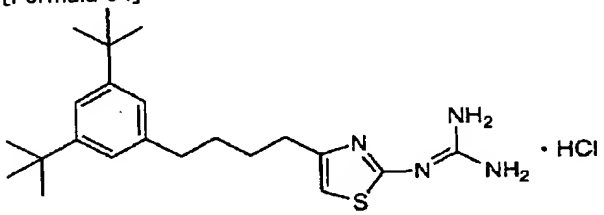
[0165] Using the compound manufactured in the example 11 of reference, it was operated like the example of example of reference 7 -> reference 8 -> example 1, and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.33 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 7.02 (2H, s), 6.46 (1H, s), 3.67 (3H, s), 2.66 (2H, t), 2.55 (2H, t), 1.73-1.65 (4H, m), 1.41 (18H, s).
[0166] Example 1 (2)
[Formula 92]



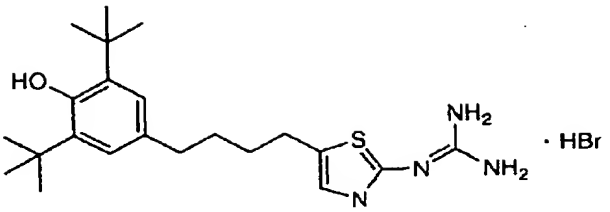
[0167] Using the corresponding aldehyde, it was operated like the example of example of example of example of example of example of example of example of example of reference 1 -> reference 2 -> reference 3 -> reference 4 -> reference 5 -> reference 6 -> reference 7 -> reference 8 -> reference 9 -> example 1, and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.34 (acetic acid: ethyl acetate : water = 20:1:1), NMR(CDCl3): delta 6.91 (1H, d), 6.79 (1H, d), 6.45 (1H, s), 4.89 (1H, s), 2.64 (2H, t), 2.52 (2H, t), 2.24 (3H, s), 1.68-1.58 (4H, m), 1.39 (9H, s).
[0168] Example 1 (3)
[Formula 93]



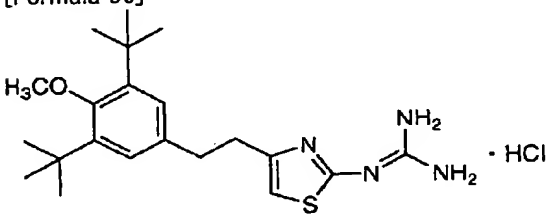
[0169] Using the corresponding aldehyde, it was operated like the example of example of example of example of example of example of example of example of example of reference 1 -> reference 2 -> reference 3 -> reference 4 -> reference 5 -> reference 6 -> reference 10 -> reference 11 -> reference 7 -> reference 8 -> example 1, and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.35 (acetic acid: ethyl acetate : water = 20:1:1), NMR(CDCl3): delta 6.94 (1H, d), 6.85 (1H, d), 6.46 (1H, s), 3.75 (3H, s), 2.66 (2H, t), 2.54 (2H, t), 2.29 (3H, s), 1.70-1.60 (4H, m), 1.37 (9H, s).
[0170] Example 1 (4)
[Formula 94]



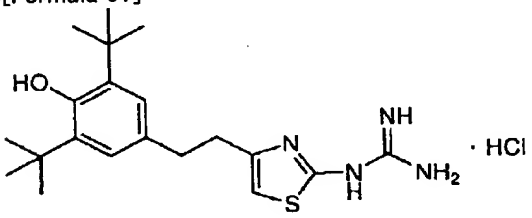
[0171] Using the corresponding aldehyde, it was operated like the example of example of example of example of example of example of example of example of reference 1 -> reference 3 -> reference 4 -> reference 5 -> reference 6 -> reference 7 -> reference 8 -> example 1, and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.44 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 7.25 (1H, s), 7.02 (2H, d), 6.44 (1H, s), 2.70-2.58 (4H, m), 1.75-1.60 (4H, m), 1.30 (18H, s).
[0172] Example 1 (5)
[Formula 95]



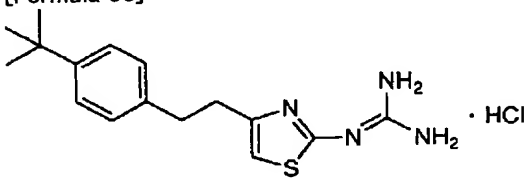
[0173] The title compound which operates it like an example 1 and has the following physical-properties value was obtained using the compound manufactured in the example 25 of reference.
TLC:Rf 0.49 (methanol: chloroform : acetic-acid = 20:2:1) and NMR(CD3OD):delta 7.12 (1H, s), 6.93 (2H, s), 2.80 (2H, t), 2.54 (2H, t), 1.73-1.52 (4H, m), 1.41 (18H, s).
[0174] Example 1 (6)
[Formula 96]



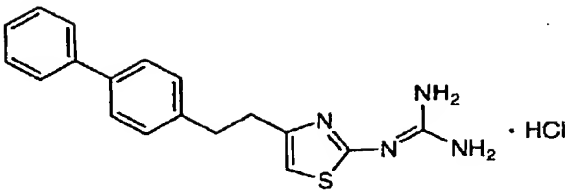
[0175] Using the compound manufactured in the example 1 of reference, it was operated like the example of example of example of example of reference 11 -> reference 6 -> reference 7 -> reference 8 -> example 1, and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.73 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 7.04 (2H, s), 6.22 (1H, s), 3.67 (3H, s), 2.88 (4H, s), 1.41 (18H, s).
[0176] Example 1 (7)
[Formula 97]



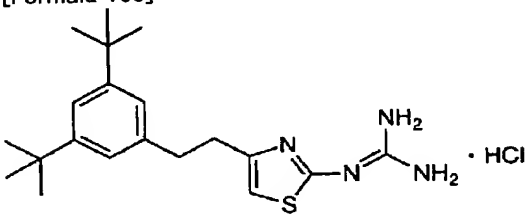
[0177] Using the compound manufactured in the example 2 of reference, it was operated like the example of example of example of example of reference 6 -> reference 7 -> reference 8 -> reference 9 -> example 1, and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.78 (acetic acid: ethyl acetate : water = 12:2:1) and NMR(DMSO-d6):delta 8.28-8.25 (4H, m), 6.87 (2H, s), 6.69 (1H, s), 2.84 (4H, s), 1.35 (18H, s).
[0178] Example 1(8) -1 (11)
Using the corresponding aldehyde, it was operated like the example of example of example of example of reference 1 -> reference 6 -> reference 7 -> reference 8 -> example 1, and the following compound was obtained.
[0179] Example 1 (8)
[Formula 98]



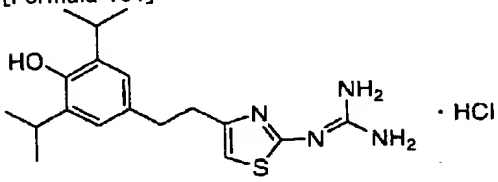
[0180] TLC:Rf 0.37 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3+CD3OD (one drop)):delta 7.33-7.28 (2H, m), 7.12-7.10 (2H, m), 6.47 (1H, s), 2.93 (4H, s), 1.30 (9H, s).
[0181] Example 1 (9)
[Formula 99]



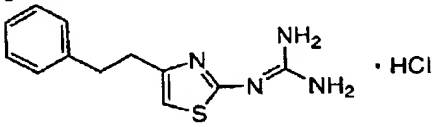
[0182] TLC:Rf 0.35 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CD3OD):delta 7.90-7.25 (9H, m), 6.74 (1H, s), 3.04 (4H, s).
[0183] Example 1 (10)
[Formula 100]



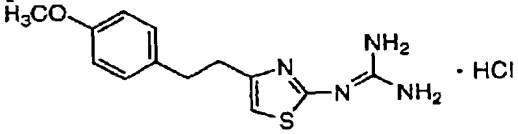
[0184] TLC:Rf 0.37 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 7.26 (1H, s), 7.00 (2H, d), 6.47 (1H, s), 2.94 (4H, s), 1.31 (18H, s).
[0185] Example 1 (11)
[Formula 101]



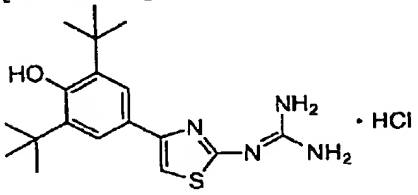
[0186] TLC:Rf 0.39 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 6.79 (2H, s), 6.47 (1H, s), 5.16 (1H, s), 3.28-3.14 (2H, m), 2.93-2.86 (4H, m), 1.22 (12H, d).
[0187] Example 1 (12) - (20)
Using the corresponding carboxylic acid, it was operated like the example of reference 8 -> example 1, and the following compound was obtained.
[0188] Example 1 (12)
[Formula 102]



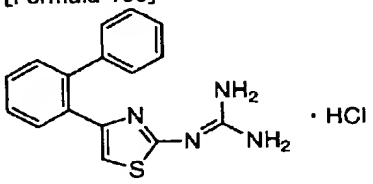
[0189] TLC:Rf 0.44 (acetic acid: ethyl acetate : water = 20:2:1) and NMR(CDCl3:CD3OD=20:1):delta 7.31-7.14 (5H, m), 6.33 (1H, s), 3.45 (4H, s).
[0190] Example 1 (13)
[Formula 103]



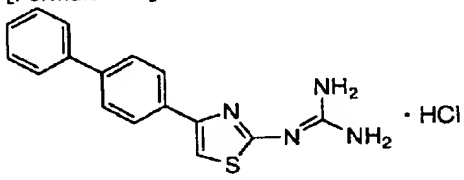
[0191] TLC:Rf 0.43 (acetic acid: ethyl acetate : water = 20:2:1) and NMR(CDCl3:CD3OD=20:1):delta 7.09-6.80 (4H, m), 6.41 (1H, s), 3.79 (4H, s), 2.90 (2H, s).
[0192] Example 1 (14)
[Formula 104]



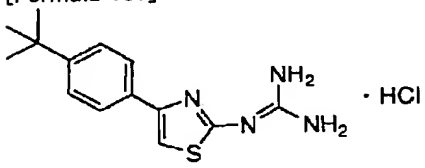
[0193] TLC:Rf 0.55 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 7.58 (2H, s), 6.68 (1H, s), 1.46 (18H, s).
[0194] Example 1 (15)
[Formula 105]



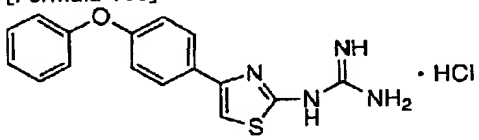
[0195] TLC:Rf 0.64 (methanol: chloroform : acetic-acid = 16:3:1) and NMR(DMSO-d6):delta 12.35 (1H, brs), 7.89 (4H, brs), 7.75 (1H, m), 7.48 (2H, t), 7.34 (4H, m), 7.17 (2H, m), 7.08 (1H, s).
[0196] Example 1 (16)
[Formula 106]



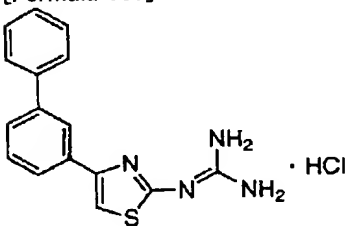
[0197] TLC:Rf 0.65 (methanol: chloroform : acetic-acid = 8:1:1) and NMR(DMSO-d6):delta 12.63 (1H, brs), 8.36 (4H, brs), 8.05 (2H, d), 7.83 (1H, s), 7.74 (4H, m), 7.45 (3H, m).
[0198] Example 1 (17)
[Formula 107]



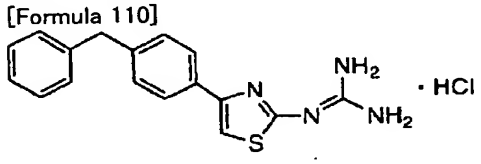
[0199] TLC:Rf 0.76 (methanol: chloroform : acetic-acid = 16:3:1) and NMR(DMSO-d6):delta 12.58 (1H, brs), 8.34 (4H, brs), 7.85 (2H, d), 7.68 (1H, s), 7.45 (2H, d, J= 8Hz), 1.31 (9H, s).
[0200] Example 1 (18)
[Formula 108]



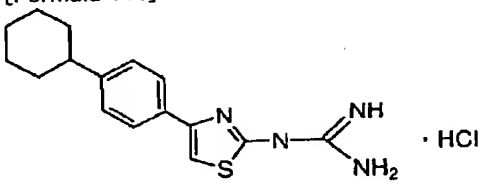
[0201] TLC:Rf 0.49 (methanol: chloroform : acetic-acid = 18:1:1) and NMR(DMSO-d6):delta 12.60 (1H, brs), 8.27 (4H, brs), 7.97 (2H, dd), 7.66 (1H, s), 7.42 (2H, m), 7.18 (2H, m), 7.06 (4H, m).
[0202] Example 1 (19)
[Formula 109]



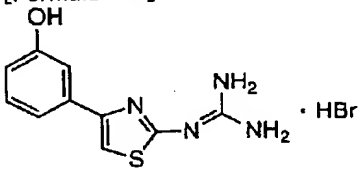
[0203] TLC:Rf 0.38 (methanol: chloroform : acetic-acid = 18:1:1) and NMR(DMSO-d6):delta 12.67 (1H, brs), 8.37 (4H, brs), 8.18 (1H, s), 7.99-7.91 (2H, m), 7.78-7.36 (7H, m).
[0204] Example 1 (20)
[Formula 110]



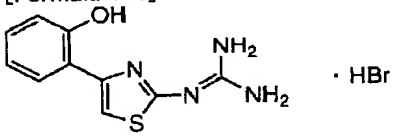
[0205] TLC:Rf 0.39 (methanol: chloroform : acetic-acid = 18:1:1) and NMR(DMSO-d6):delta 12.57 (1H, brs), 8.32 (4H, brs), 7.85 (2H, d), 7.68 (1H, s), 7.34-7.19 (7H, m), 3.98 (2H, s).
[0206] Example 1 (21)
[Formula 111]



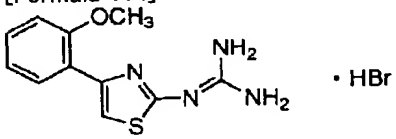
[0207] TLC:Rf 0.40 (methanol: chloroform : acetic-acid = 18:1:1) and NMR(DMSO-d6):delta 12.67 (1H, brs), 8.37 (4H, brs), 7.85 (2H, d), 7.67 (1H, s), 7.27 (2H, d), 2.51 (1H, m), 1.78 (5H, m), 1.40 (5H, m).
[0208] Example 1 (22)
[Formula 112]



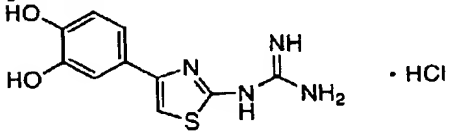
[0209] Using the compound manufactured in the example 12 of reference, it was operated like the example 1 and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.51 (methanol: chloroform : acetic-acid = 15:4:1) and NMR(DMSO-d6):delta 11.99 (1H, brs), 9.52 (1H, s), 8.27 (4H, s), 7.66 (1H, s), 7.27 (3H, m), 6.78 (1H, m).
[0210] Example 1 (23)
[Formula 113]



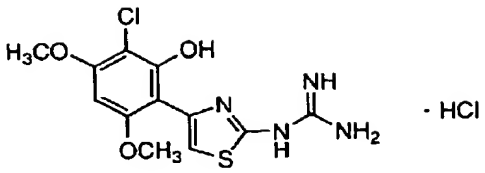
[0211] Using the compound manufactured in the example 14 of reference, it was operated like the example 1 and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.64 (methanol: chloroform : acetic-acid = 15:4:1) and NMR(DMSO-d6):delta 11.91 (1H, brs), 10.27 (1H, s), 8.23 (4H, s), 7.96 (1H, dd), 7.81 (1H, s), 7.17 (1H, m), 6.93 (2H, m).
[0212] Example 1(24) -1 (28)
A 2-BUROMO-3'-methoxy acetophenone, 4-(chloro acetyl) catechol, 2, 3'-dichloro - Using a 4' and 6'-dimethoxy-2'-hydroxy acetophenone, 2-chloroacetophenone, or 2-BUROMO-2'-acetonaphthone, it was operated like the example 1, respectively and the following compound was obtained.
[0213] Example 1 (24)
[Formula 114]



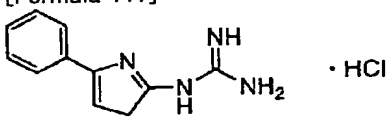
[0214] TLC:Rf 0.68 (methanol: chloroform : acetic-acid = 15:4:1) and NMR(DMSO-d6):delta 11.95 (1H, brs), 8.24 (4H, s), 8.04 (1H, d), 7.77 (1H, s), 7.36 (1H, m), 7.09 (2H, m), 3.93 (3H, s).
[0215] Example 1 (25)
[Formula 115]



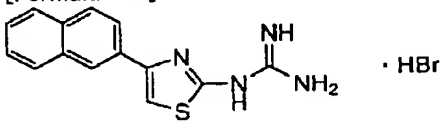
[0216] TLC:Rf 0.22 (methanol: chloroform : acetic-acid = 15:2:1) and NMR(DMSO-d6):delta 12.51 (1H, br), 9.25 (1H, brs), 9.04 (1H, brs), 8.35 (4H, brs), 7.39 (1H, s), 7.29 (1H, d), 7.21 (1H, dd), 6.79 (1H, d).
[0217] Example 1 (26)
[Formula 116]



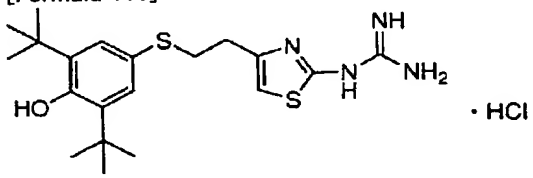
[0218] TLC:Rf 0.46 (chloroform: methanol =9:1) and NMR(DMSO-d6):delta 13.75 (1H, brs), 7.23 (1H, s), 6.49 (4H, brs), 6.36 (1H, s), 3.92 (3H, s), 3.89 (3H, s).
[0219] Example 1 (27)
[Formula 117]



[0220] TLC:Rf 0.53 (methanol: chloroform : acetic-acid = 16:3:1) and NMR(DMSO-d6):delta 12.68 (1H, brs), 8.36 (4H, s), 7.96 (2H, d), 7.76 (1H, s), 7.50-7.30 (3H, m).
[0221] Example 1 (28)
[Formula 118]

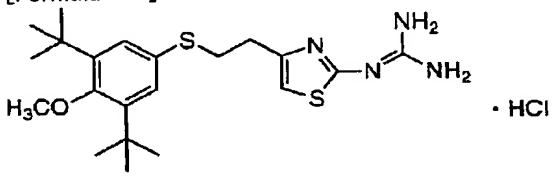


[0222] TLC:Rf 0.60 (methanol: chloroform : acetic-acid = 16:3:1) and NMR(DMSO-d6):delta 12.04 (1H, brs), 8.55 (1H, s), 8.29 (4H, brs), 8.15-7.85 (5H, m), 7.63-7.45 (2H, m).
[0223] Example 1 (29)
[Formula 119]

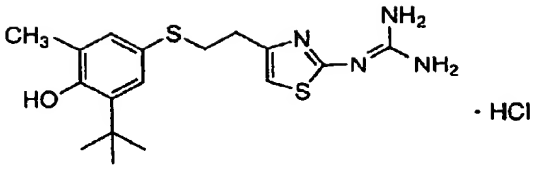


[0224] Using the compound manufactured in the example 18 of reference, it was operated like the example 8 of reference, and the example 1, and the title compound which has the following physical-properties value was obtained.

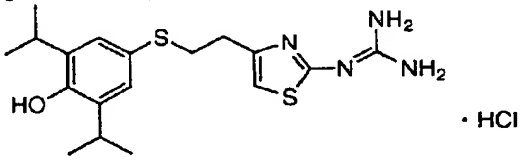
TLC:Rf 0.62 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 7.23 (2H, s), 6.44 (1H, s), 3.10 (2H, t), 2.92 (2H, t), 1.42 (18H, s).
[0225] Example 1 (30)
[Formula 120]



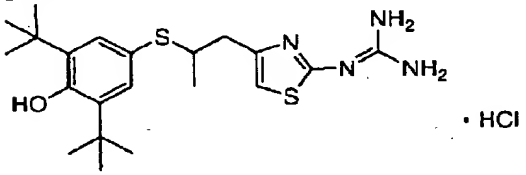
[0226] Using the compound manufactured in the example 17 of reference, it was operated like the example of example of example of reference 11 -> reference 18 -> reference 8 -> example 1, and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.37 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 7.24 (2H, s), 6.57 (1H, s), 3.68 (3H, s), 3.15 (2H, t), 2.98 (2H, t), 1.41 (18H, s).
[0227] Example 1(31) -1 (32)
Using the corresponding compound, it was operated like the example of example of example of example of example of reference 15 -> reference 16 -> reference 17 -> reference 18 -> reference 8 -> example 1, and the following compound was obtained.
[0228] Example 1 (31)
[Formula 121]



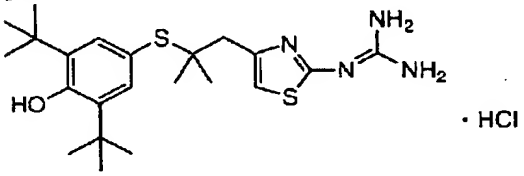
[0229] TLC:Rf 0.41 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3+CD3OD (one drop)):delta 7.15 (1H, d), 7.00 (1H, d), 6.56 (1H, s), 3.10 (2H, t), 2.90 (2H, t), 2.21 (3H, s), 1.38 (9H, s).
[0230] Example 1 (32)
[Formula 122]



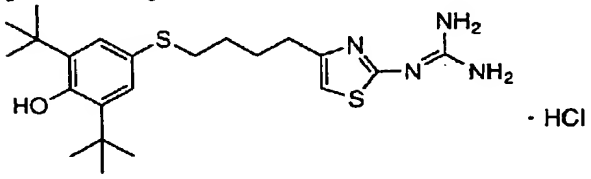
[0231] TLC:Rf 0.43 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 7.09 (2H, s), 6.54 (1H, s), 3.19-3.07 (4H, m), 2.94-2.85 (2H, m), 1.25 (12H, d).
[0232] Example 1(33) -1 (34)
Using the compound and the corresponding carboxylic-acid derivative which were manufactured in the example 16 of reference, it was operated like the example of example of reference 18 -> reference 8 -> example 1, and the following compound was obtained.
[0233] Example 1 (33)
[Formula 123]



[0234] TLC:Rf 0.53 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 7.25 (2H, s), 6.57 (1H, s), 5.29 (1H, s), 3.33 (1H, m), 2.95 (1H, dd), 2.72 (1H, dd), 1.42 (18H, s), 1.25 (3H, d).
[0235] Example 1 (34)
[Formula 124]

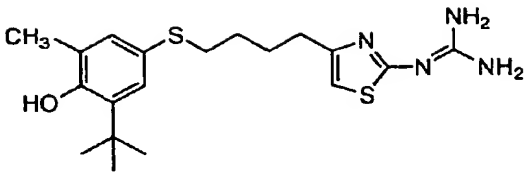


[0236] TLC:Rf 0.46 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 7.33 (2H, s), 6.63 (1H, s), 5.37 (1H, s), 2.85 (2H, s), 1.44 (18H, s), 1.21 (6H, s).
[0237] Example 1 (35)
[Formula 125]

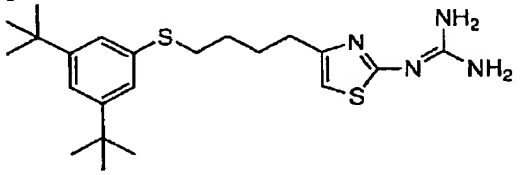


[0238] Using the compound manufactured in the example 19 of reference, it was operated like the example 8 of reference, and the example 1, and the title compound which has the following physical-properties value was obtained.

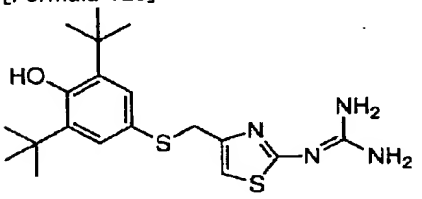
TLC:Rf 0.44 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CD3OD):delta 7.20 (2H, s), 6.71 (1H, s), 2.82 (2H, t), 2.68 (2H, t), 1.81 (2H, m), 1.62 (2H, m), 1.40 (18H, s).
[0239] Example 1(36) -1 (37)
Using the corresponding compound, it was operated like the example of example of example of example of reference 15 -> reference 16 -> reference 19 -> reference 8 -> example 1, and the following compound was obtained.
[0240] Example 1 (36)
[Formula 126]



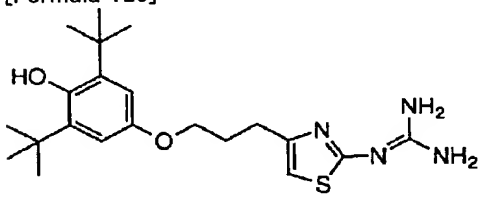
[0241] TLC:Rf 0.42 (acetic acid: ethyl acetate : water = 20:1:1), NMR(CDCl3): delta 7.17 (1H, d), 7.04 (1H, d), 6.43 (1H, s), 5.06 (1H, s), 2.81 (2H, t), 2.61 (2H, t), 2.23 (3H, s), 1.80–1.56 (4H, m), 1.36 (9H, s).
[0242] Example 1 (37)
[Formula 127]



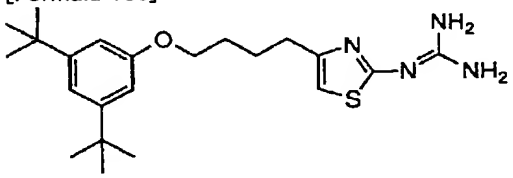
[0243] TLC:Rf 0.39 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 7.24 (1H, d), 7.18 (2H, d), 6.45 (1H, s), 2.95 (2H, t), 2.65 (2H, t), 1.85–1.65 (4H, m), 1.31 (18H, s).
[0244] Example 1 (38)
[Formula 128]



[0245] Using the compound and the corresponding carboxylic-acid derivative which were manufactured in the example 16 of reference, it was operated like the example of example of reference 19 -> reference 8 -> example 1, and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.57 (chloroform: methanol =10:1) and NMR(CDCl3:CD3OD=10:1):delta 7.14 (2H, s), 6.48 (1H, s), 3.93 (2H, s), 1.39 (18H, s).
[0246] Example 1 (39)
[Formula 129]

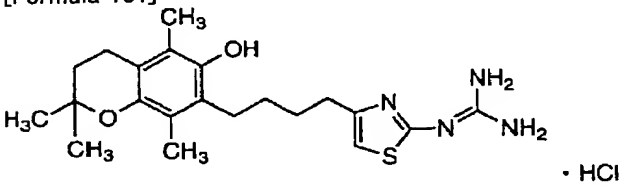


[0247] Using the compound manufactured in the example 20 of reference, it was operated like the example of example of example of example of reference 2 -> reference 7 -> reference 8 -> reference 9 -> example 1, and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.35 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3):delta 6.74 (2H, s), 6.32 (1H, s), 3.94 (2H, t), 3.49 (1H, s), 2.79 (2H, t), 2.11 (2H, m), 1.42 (18H, s).
[0248] Example 1 (40)
[Formula 130]

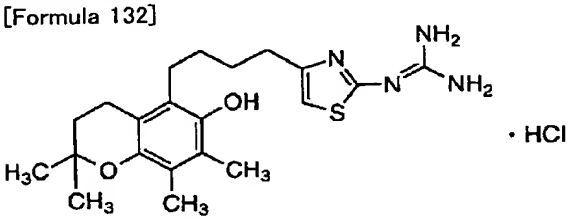


[0249] Using the corresponding compound, it was operated like the example of example of example of reference 20 -> reference 7 -> reference 8 -> example 1, and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.40 (acetic acid: ethyl acetate : water = 20:1:1) and NMR(CDCl3+CD3OD (one drop)):delta 7.02 (1H, d), 6.75 (2H, d), 6.53 (1H, s), 4.00 (2H, t), 2.72 (2H, t), 1.88–1.80 (4H, m), 1.31 (18H, s).

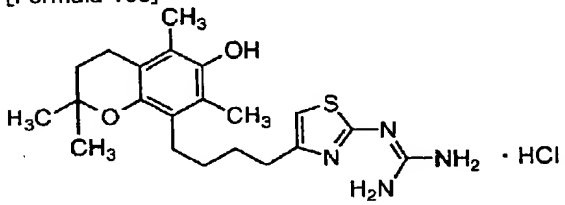
[0250] Example 1(41) -1 (43)
The compound indicated by the PCT application number JP 95/No. 294 specification, 7-(2-formyl ethyl)-6-methoxymethyloxy - 2, 2, 5, a 8-tetramethyl chroman, 5-(2-formyl ethyl)-6-methoxymethyloxy - A 2, 2, 7, and 8-tetramethyl chroman or 8-(2-formyl ethyl)-6-methoxymethyloxy - A 2, 2, 5, and 7-tetramethyl chroman is used. It is operated like the example of example of example of example of example of reference 5 -> reference 6 -> reference 7 -> reference 8 -> reference 9 -> example 1, respectively. The following compound was obtained.
[0251] Example 1 (41)
[Formula 131]



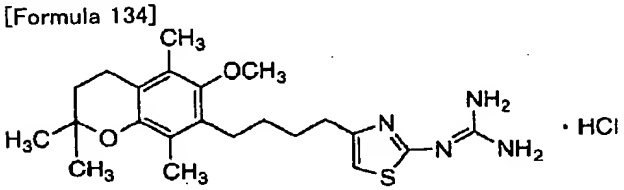
[0252] TLC:Rf 0.55 (methanol: chloroform : acetic-acid = 15:2:1) and NMR(CD3OD):delta 6.75 (1H, s), 2.76-2.53 (6H, m), 2.08 (3H, s), 2.03 (3H, s), 1.85-1.65 (4H, m), 1.60-1.40 (2H, m), 1.24 (6H, s).
[0253] Example 1 (42)
[Formula 132]



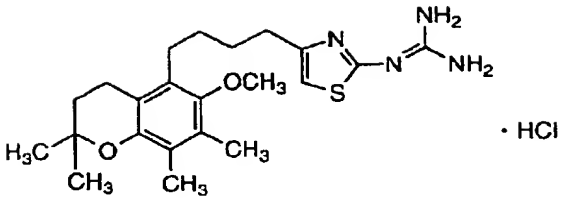
[0254] TLC:Rf 0.41 (methanol: chloroform : acetic-acid = 20:2:1) and NMR(CD3OD):delta 6.75 (1H, s), 2.77-2.53 (6H, m), 2.12 (3H, s), 2.04 (3H, s), 1.85-1.67 (4H, m), 1.60-1.40 (2H, m), 1.26 (6H, s).
[0255] Example 1 (43)
[Formula 133]



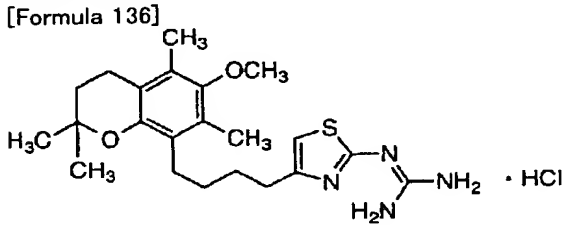
[0256] TLC:Rf 0.37 (methanol: chloroform : acetic-acid = 20:2:1) and NMR(CD3OD):delta 6.71 (1H, s), 2.78-2.53 (6H, m), 2.14 (3H, s), 2.09 (3H, s), 1.83-1.60 (4H, m), 1.60-1.38 (2H, m), 1.22 (6H, s).
[0257] Example 1(44) -1 (46)
The compound which it is indicated by the PCT application number JP 95/No. 294 specification, or was manufactured using the method of a publication on the specifications, 7-(2-formyl ethyl)-6-methoxy - 2, 2, 5, a 8-tetramethyl chroman, 5-(2-formyl ethyl)-6-methoxy - A 2, 2, 7, and 8-tetramethyl chroman or 8-(2-formyl ethyl)-6-methoxy - A 2, 2, 5, and 7-tetramethyl chroman is used. It is operated like the example of example of example of example of reference 5 -> reference 6 -> reference 7 -> reference 8 -> example 1, respectively. The following compound was obtained.
[0258] Example 1 (44)
[Formula 134]



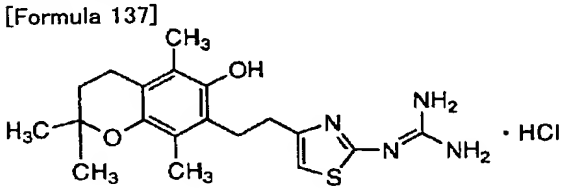
[0259] TLC:Rf 0.60 (methanol: chloroform : acetic-acid = 15:2:1) and NMR(CD3OD):delta 6.73 (1H, s), 3.62 (3H, s), 2.78-2.55 (6H, m), 2.12 (3H, s), 2.04 (3H, s), 1.86-1.67 (4H, m), 1.60-1.40 (2H, m), 1.27 (6H, s).
[0260] Example 1 (45)
[Formula 135]



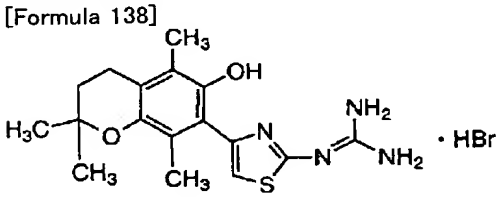
[0261] TLC:Rf 0.38 (methanol: chloroform : acetic-acid = 20:2:1) and NMR(CD3OD):delta 6.76 (1H, s), 3.61 (3H, s), 2.78-2.53 (6H, m), 2.14 (3H, s), 2.04 (3H, s), 1.83-1.65 (4H, m), 1.62-1.38 (2H, m), 1.27 (6H, s).
[0262] Example 1 (46)
[Formula 136]



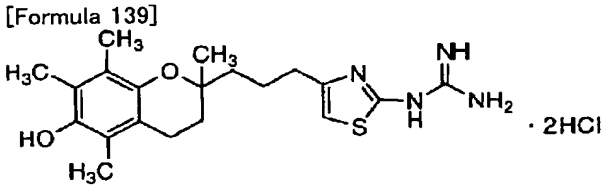
[0263] TLC:Rf 0.37 (methanol: chloroform : acetic-acid = 20:2:1) and NMR(CD3OD):delta 6.69 (1H, s), 3.60 (3H, s), 2.75-2.53 (6H, m), 2.17 (3H, s), 2.12 (3H, s), 1.83-1.65 (4H, m), 1.60-1.38 (2H, m), 1.23 (6H, s).
[0264] Example 1 (47)
[Formula 137]



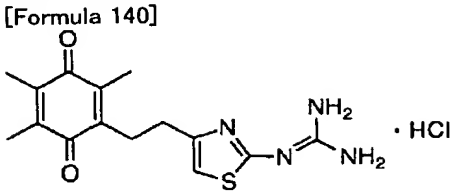
[0265] 7-(2-methoxy carbonylethyl)-6-methoxymethyloxy indicated by the PCT application number JP 95/No. 294 specification - Using the 2, 2, 5, and 8-tetramethyl chroman, it was operated like the example of example of reference 8 -> reference 9 -> example 1, and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.43 (methanol: chloroform : acetic-acid = 15:2:1), NMR(CDCl3+CD3OD): delta 8.31-8.03 (1H, br), 6.74 (1H, s), 3.07-2.91 (2H, m), 2.91-2.72 (2H, m), 2.62 (2H, t), 2.12 (3H, s), 2.08 (3H, s), 1.80 (2H, t), 1.28 (6H, s).
[0266] Example 1 (48)
[Formula 138]

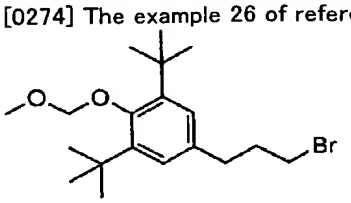


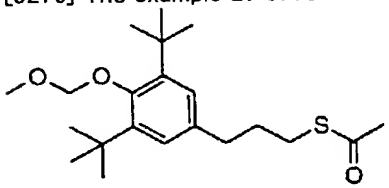
[0267] 7-acetyl-6-methoxymethyloxy indicated by the PCT application number JP 95/No. 294 specification - Using the 2, 2, 5, and 8-tetramethyl chroman, it was operated like the example of example of example of reference 10 -> reference 13 -> reference 14 -> example 1, and the title compound which has the following physical-properties value was obtained.
[0268] TLC:Rf 0.56 (methanol: chloroform : acetic-acid = 30:4:1), NMR(DMSO-d6): delta 11.87 (1H, brs), 8.17 (4H, brs), 7.46 (1H, brs), 7.15 (1H, brs), 2.61 (2H, t), 2.06 (3H, s), 1.87 (3H, s), 1.76 (2H, t), 1.25 (6H, s).
[0269] Example 1 (49)
[Formula 139]

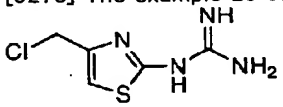


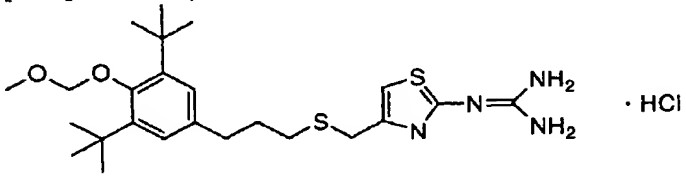
[0270] Using the 2-(3-carboxy propyl)-2, 5 and 7, and 8-tetramethyl-6-methoxymethyloxy chroman indicated by the JP,3-204874,A specification, it was operated like the example of example of reference 8 -> reference 9 -> example 1, and the title compound which has the following physical-properties value was obtained.
[0271] TLC:Rf 0.42 (acetic acid: ethyl acetate : water = 20:2:1), NMR(DMSO-d6): delta 12.30 (1H, brs) 8.27 (4H, brs), 7.37 (1H, brs), 6.86 (1H, s), 2.59 (2H, t), 2.04 (3H, s), 2.01 (3H, s), 1.97 (3H, s), 1.9-1.6 (4H, m), 1.6-1.3 (2H, m), 1.16

(3H, s).
[0272] Example 1 (50)
[Formula 140]


[0273] Using the compound manufactured in the example 21 of reference, it was operated like the example of reference 8 -> example 1, and the title compound which has the following physical-properties value was obtained.
TLC:Rf 0.51 (acetic acid: ethyl acetate : water = 12:2:1) and NMR(DMSO-d6):delta 12.44 (1H, brs), 8.29 (4H, brs), 6.93 (1H, s), 2.9-2.6 (4H, m), 1.95 (6H, s), 1.84 (3H, s).
[0274] The example 26 of reference [Formula 141]


[0275] Triphenyl phosphine (1.57g), a sodium hydrogencarbonate (1.26g), and carbon tetrabromide (2.49g) were added to the methylene chloride solution (50ml) of 3-(3, 5-G t-butyl-4-methoxymethyloxy phenyl) propanol (1.53g) manufactured like the example 6 of reference using the compound manufactured in the example 3 of reference. Mixture was agitated at the room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, sequential washing was carried out with a saturation sodium hydrogencarbonate, water, and saturation brine, and it condensed after desiccation with magnesium sulfate. Hexane-ethyl acetate washed the residue and the obtained filtrate was condensed. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:10), and the title compound (1.46g) which has the following physical-properties value was obtained.
TLC:Rf 0.58 (ethyl acetate: n-hexane =1:10).
[0276] The example 27 of reference [Formula 142]


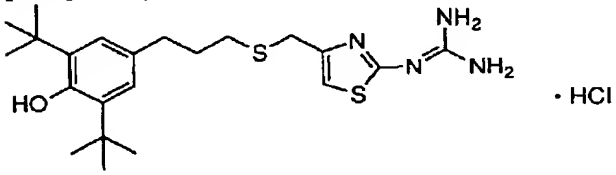
[0277] Thioacetic-acid sodium (676mg) was added to the acetone solution (10ml) of the compound (1.46g) manufactured in the example 26 of reference. Mixture was flowed back for 4 hours. It flowed into water after cooling a reaction solution, and ethyl acetate extracted. Water and saturation brine washed the organic layer and it condensed after desiccation with the sodium sulfate. The residue was refined by column chromatography (ethyl acetate: n-hexane =1:30), and the title compound (1.45g) which has the following physical-properties value was obtained.
TLC:Rf 0.38 (ethyl acetate: n-hexane =1:10).
[0278] The example 28 of reference [Formula 143]


[0279] The acetone solution (6ml) of 1 and 3-dichloroacetone (1.8g) was added to the acetone suspension (7.5ml) of amidino thiourea (1.68g). Mixture was agitated at the room temperature overnight. The acetone washed the depositing crystal, it recrystallized in ethanol, and the title compound (1.61g) which has the following physical-properties value was obtained.
TLC:Rf 0.60 (methanol: chloroform : acetic-acid = 15:2:1).
[0280] The example 29 of reference [Formula 144]


[0281] Under the argon, it added little by little, and to it, sodium (46mg) was agitated until it dissolved in ethanol (5ml). The ethanol solution (5ml) of the compound (366mg) manufactured in the example 27 of reference was added to the ethanol solution of the prepared ethoxy sodium under 0 degree C and an argon. The mixed solution was agitated for 30 minutes at 0 degree C. The ethanol solution (5ml) of the compound (114mg) manufactured in the example 28 of reference was slowly dropped at the reaction solution. The mixed solution was agitated at the room temperature for 3 hours. Furthermore, the ethanol solution (5ml) of the compound (100mg) manufactured in the example 28 of reference was dropped. The mixed solution was agitated at the room temperature for 16 hours. The sludge was ****(ed) and the filtrate was condensed. The residue was refined by column chromatography (chloroform: methanol =30:1 ->10:1), and the title compound (480mg) which has the following physical-properties value was obtained.

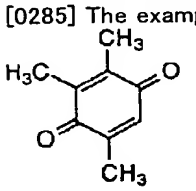
[0282] TLC:Rf 0.85 (methanol: chloroform : acetic-acid = 15:2:1), NMR(CDCl3): delta 7.04 (2H, s), 6.33 (1H, s), 4.88 (2H, s), 3.63 (3H, s), 2.63 (2H, t), 2.53 (2H, t), 1.88 (2H, quint), 1.78-1.55 (2H, br), 1.43 (18H, s).

[0283] Example 2 [Formula 145]



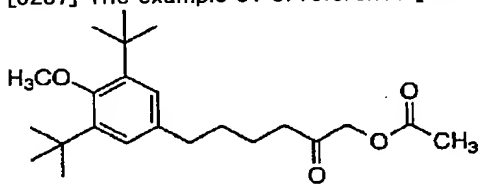
[0284] The compound (450mg) manufactured in the example 29 of reference was operated like the example 9 of reference, and the title compound (408mg) which has the following physical-properties value was obtained.
TLC:Rf 0.30 (chloroform: methanol =10:1) and NMR(DMSO-d6):delta 12.85 (1H, br), 8.35 (3H, brs), 6.95 (1H, s), 6.88 (1H, s), 6.70 (1H, s), 3.73 (2H, s), 2.60-2.43 (2H, m), 1.35 (18H, s).

[0285] The example 30 of reference [Formula 146]



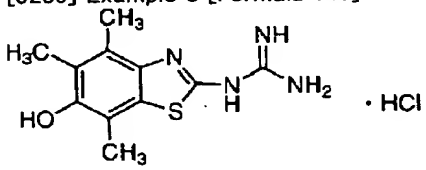
[0286] Water (80ml) and palladium (IV) acetate (5.1g) were added to the THF solution (80ml) of 2, 3, and 5-trimethyl hydroquinone (1.52g). The heating reflux of the mixture was carried out for 30 minutes. 2-N sodium hydroxide was added to the reaction mixture, and the ether extracted. Water and saturation brine washed the organic layer, it condensed after desiccation with magnesium sulfate, and the title compound (1.32g) was obtained.

[0287] The example 31 of reference [Formula 147]



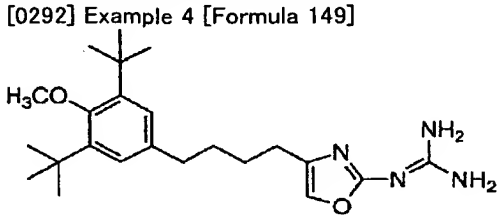
[0288] The acetone solution (10ml) of the 6-(3, 5-G t-butyl-4-methoxypheny)-alpha-chloro-2-hexanone (200mg) and potassium acetate (111mg) which were manufactured like the example 7 of reference and the example 8 of reference was agitated at 65 degrees C for 17 hours using the compound manufactured in the example 11 of reference. The reaction solution was condensed and it diluted with ethyl acetate. The organic layer was condensed after desiccation with magnesium sulfate by washing water and saturation brine, and the title compound (1.32g) which has the following physical-properties value was obtained.
TLC:Rf 0.33 (hexane: ethyl-acetate =5:1).

[0289] Example 3 [Formula 148]



[0290] Concentrated hydrochloric acid (0.134ml) was added to the ethanol solution (10ml) of guanidyl thiourea (520mg). The ethanol solution (20ml) of the compound (1.32g) manufactured in the example 30 of reference was added to mixture. Mixture was agitated for two days at the room temperature. The reaction mixture was filtered and the crystal was washed by the acetonitrile. The filtrate was condensed and the residue was recrystallized with ethanol and the ether. Sequential washing of the depositing crystal was carried out with an acetonitrile, ethanol, and the ether, it dried and the title compound (254mg) which has the following physical-properties value was obtained.

[0291] TLC:Rf 0.18 (chloroform: methanol =5:1) and NMR(DMSO-d6):delta 12.6 (1H, brs), 8.51 (1H, s), 8.37 (4H, s), 2.47 (3H, s), 2.30 (3H, s), 2.21 (3H, s).
[0292] Example 4 [Formula 149]



[0293] 5-N solution of hydrochloric acid (1.8ml) was added to the compound (170mg) manufactured in the example 31 of reference, and the dioxane solution (9ml) of a dicyandiamide (380mg), and it condensed after 20-hour churning at the room temperature. The residue was refined by column chromatography (1:10 ->5:1 -> chloroform: ethyl acetate: n-hexane = methanol = 30:1->10:1), and the title compound (51mg) which has the following physical-properties value was obtained.
[0294] TLC:Rf 0.50 (chloroform: methanol =9:1) and NMR(CDCl3):delta 7.03 (2H, s), 6.92 (1H, s), 5.95 (4H, brs), 3.67 (3H, s), 2.55 (2H, t), 2.45 (2H, t), 1.67 (4H, m), 1.42 (18H, s).
[0295]
[Example(s) of Production]
It tableted, after mixing each one or less example [of pharmaceutical preparation] component with a conventional method, and tablet 100 lock which has a 50mg active ingredient in 1 lock was obtained.
- 4-(4-(3, 5-G t-butyl-4-hydroxyphenyl) butyl)-2-guanidyl thiazole --- 5.0g and calcium carboxymethyl cellulose (disintegrator) --- 0.2g and magnesium stearate (lubricant) --- 0.1g and microcrystal cellulose --- 4.7g [0296] After mixing each two or less example [of pharmaceutical preparation] component with a conventional method, the solution was sterilized with the conventional method, and it filled up ampul with 5ml at a time, and freeze-dried with the conventional method, and 100 ampul which contains a 20mg active ingredient among 1 ampul was obtained.
- 4-(4-(3, 5-G t-butyl-4-hydroxyphenyl) butyl)-2-guanidyl thiazole --- 2.0g and mannitol --- 200mg and distilled water --- 500ml

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[Translation done.]

(19)日本国特許庁(JP)

(12)公開特許公報（A）

(11)特許出願公開番号

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	263/48			263/48	
	263/58			263/58	
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(71)出願人　000185983
小野薬品工業株式会社
大阪府大阪市中央区道修町2丁目1番5号

(72)発明者　松井　敏明
大阪府三島郡島本町桜井3丁目1番1号　小野薬品工業株式会社水無瀬研究所内

(72)発明者　辰巳　正
大阪府三島郡島本町桜井3丁目1番1号　小野薬品工業株式会社水無瀬研究所内

(72)発明者　大内田　修一
大阪府三島郡島本町桜井3丁目1番1号　小野薬品工業株式会社水無瀬研究所内

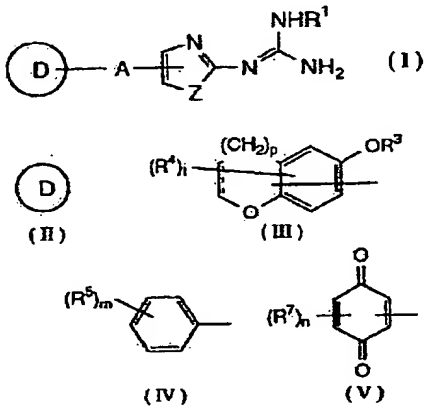
(74)代理人　弁理士　大家　邦久

(54)【発明の名称】グアニジル誘導体

(57)【要約】

【構成】　式（Ｉ）の化合物及びその塩（式中、Ｚは Ｓ、Ｏ、NR^2（R^2はＨ、アルキル）；R^1はＨ、アルキル、アシル；Ａは単結合、アルキレン等；式（II）の基は(1)式(III)の基（R^3はＨ、アルキル、アシル；R^4はアルキル）、(2)式(IV)の基（R^5はアルキル、OR^6（R^6はＨ、アルキル、アシル等）、ハロゲン、フェニル、フェニルアルキル）又はベンゼン環が縮合している前記の環、(3)式(V)の基（R^7はアルキル、フェニル、フェニルアルキル））。

【化１】



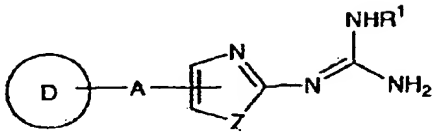
【効果】　式（Ｉ）の化合物はメイラード反応阻害作用及び／又は抗酸化作用を有し、冠動脈性心疾患、末梢循環障害、脳血管障害、糖尿病性神経症、腎症、動脈硬化、関節硬化症、白内障、網膜症、アテローム性動脈硬化症、糖尿病、心筋梗塞、炎症、消化器疾患、癌等又は過酸化脂質産生が原因となる種々の疾患（動脈硬化、糖尿病、心筋梗塞等）の治療及び／又は予防に有用である。

1

【特許請求の範囲】

【請求項１】　一般式（Ｉ）

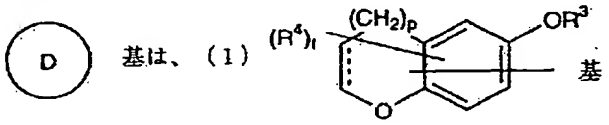
【化１】



(I)

（式中、Ｚは硫黄原子、酸素原子またはNR^2（基中、R^2は水素原子またはＣ１～４のアルキル基を表わす。）を表わし、R^1は水素原子、Ｃ１～４のアルキル基またはＣ２～５のアシル基を表わし、Ａは単結合、Ｃ１～８のアルキレン基、１個の炭素原子が１個の硫黄原子または酸素原子に置き換わっているＣ２～８のアルキレン基を表わし、

【化２】



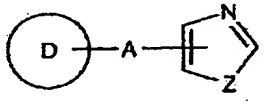
基は、（１）

基

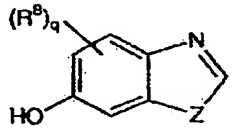
（基中、R^3は水素原子、Ｃ１～４のアルキル基またはＣ２～５のアシル基を表わし、ｌは０または１～１０を表わし、R^4はＣ１～４のアルキル基を表わし、ｐは０または１～２を表わす。）、

【化３】

式



は、式



（式中、R^5はＣ１～７のアルキル基、フェニル基またはフェニルーＣ１～４アルキル基、Ｃ５～７のシクロアルキル基またはＣ５～７のシクロアルキルーＣ１～４アルキル基を表わし、ｑは０または１～３を表わす。）を表わす。ただし、（ｉ）Ａ中、硫黄原子または酸素原子が

【化６】

に直接、結合することはなく、（ii）

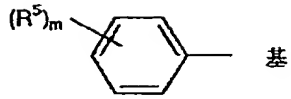
【化７】

が（１）の場合、Ａ中、硫黄原子または酸素原子が

【化８】

に直接、結合することはない。）で示されるグアニジル誘導体、それらの酸付加塩。

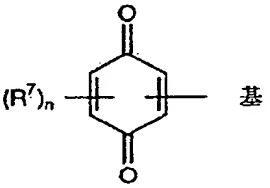
2



(2)　基

（基中、R^6はＣ１～７のアルキル基、OR^6基（基中、R^6は水素原子、Ｃ１～４のアルキル基、Ｃ２～５のアシル基、フェニル基またはフェニルーＣ１～４アルキル基を表わす。）、ハロゲン原子、フェニル基またはフェニルーＣ１～４アルキル基、Ｃ５～７のシクロアルキル基またはＣ５～７のシクロアルキルーＣ１～４アルキル基を表わし、ｍは０または１～５を表わす。）またはベンゼン環が縮合している上記の環、または

【化４】



(3)　基

（基中、R^7はＣ１～７のアルキル基、フェニル基またはフェニルーＣ１～４アルキル基、Ｃ５～７のシクロアルキル基またはＣ５～７のシクロアルキルーＣ１～４アルキル基を表わし、ｎは０または１～３を表わす。）を表わす。また、

【化５】

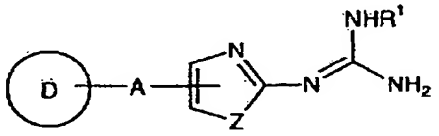
【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明は医薬として有用なグアニジル誘導体に関する。さらに詳しく言えば、本発明は

１）一般式（Ｉ）

【化９】



(I)

（式中、すべての記号は後記と同じ意味を表わす。）で示されるグアニジル誘導体、それらの酸付加塩、

２）それらの製造方法、および

３）それらを有効成分として含有する薬剤に関する。

【０００２】

【発明の背景】1912年、メイラード（Maillard）は、アミノ酸と還元糖の混合物を加熱すると褐色に着色する現象に注目して報告した［Maillard, L. C., Compt. Rend. Soc. Bio., 72, 599 (1912)］。これはアミノ酸と糖と

3

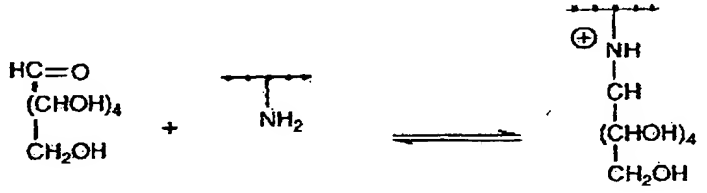
の反応によるものであり、その後この反応が生体内でも起こりうることを示唆した。1968年に至り、ラーバー（Rahbar）はヘモグロビンの小成分であるＨｂＡ１ｃが糖尿病患者において増加することを報告した［Rahbar. S., Clin. Chim. Acta., 22, 296 (1968)］。後にこのＨｂＡＩｃの化学構造はβ鎖Ｎ末端バリンにグルコースがアマドリ（Amodori）転位した型で結合していること［Kocnig, R.J., Blobstein, S.H., & Cerami, A., J. Biol. Chem., 252, 2992 (1977)］、およびこの反応は非酵素的（nonenzymatic）に起こること［Stevens, V.J., Vlassara, H., Abati, A., & Cerami, A., J. Biol. Chem., 252, 2998 (1977)］などが明らかにされたことによってメイラード反応が生体内で起こっていることが確認された。

4

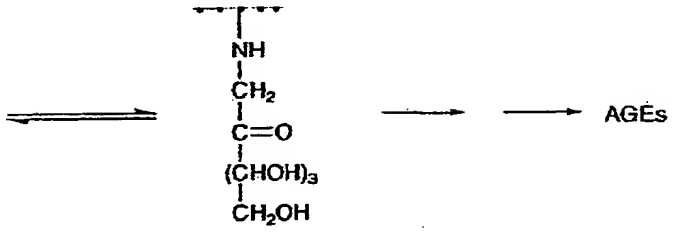
＊【０００３】メイラード反応は、その初期段階としてまず還元糖とタンパク質のアミノ基がグリコシレーション（glycosylation）を起こし、アマドリ転位生成物を形成することに始まる。これがさらに進行するとタンパク質は架橋重合［この重合物を進行したグリコシル化生成物（Advanced Glycosylation End products：ＡＧＥと略記する。）という。］し、その溶解度が低下し、プロテアーゼの作用を受けにくくなり、やがて蛍光が発生し、褐色に着色してくる。ＡＧＥ生成のメカニズムは種々提唱されているが、例えばブラウンリー(Brownlee)らによると以下の通りである（Brownlee, M. et al., Science, 232, 1629 (1986)）。

【０００４】

【化１０】



グルコース　　プロテイン　　シッフ塩基



アマドリ転位生成物

【０００５】メイラード反応は健常人においても見られる現象であるが、血糖値が上昇する糖尿病患者や、代謝回転の遅いタンパク質部位において顕著に見られる。例えば、ヘモグロビンでは糖尿病マウスは正常マウスの2.7倍のグリコシル化が起こっており［Monnier, V.M. et al., the Maillard Reaction in Foods and Nutrition, ACS Symposium Series, 215, 432, Am. Chem. Soc., Washington D.C. (1983)］、また血清アルブミンでも糖尿病患者においてはグリコシル化が亢進している［Guthrow, C.E. et al, Proc. Natl. Acad. Sci. U.S. 76, 4258 (1979)］。さらにグリコシル化した血清タンパク質をマウスに繰り返し１２週間にわたって静注すると典型的な糖尿病性腎臓障害が現れること［Monnier, V.M. et al., Clin. Endocrinol. Metab., 11, 431 (1982)］が判明している。

【０００６】眼球レンズのクリスタリンは、いったん生合成されると全く代謝回転しない特殊なタンパク質である。このクリスタリンにおいてグリコシル化が起こると、立体構造に変化が生じ、分子内ＳＨ基に酵素が関与してＳ－Ｓ結合が形成され高分子化することが認められた。ラットの糖尿病生白内障の場合、グルコースとの結合は正常の１０倍にも達し、分子内Ｓ－Ｓ結合も増加する［Monnier, V.M. & Cerami, A. Clin, Endocrinol. Metab, 11, 431 (1982)］。

【０００７】クリスタリンのグリコシル化に伴って重合、不溶性化、蛍光発生と黄色～褐色の着色が起こっており、このような変化は加齢によるレンズの変化とよく符合している［Chiou, S.H., Chylack, L.T. Jr., Tung, W.H., & Bunn, F., J. Biol. Chem. 256, 5176 (1981)］。

【０００８】結合組織に存在するコラーゲン、エラスチンはリジンとヒドロキシリジンに富むタンパク質であり、また代謝回転も遅く、腎糸球体基底膜、皮膚腱などでグルコースとの結合物の存在が見出されており［Monnier, V.M., Stevens, V.J., & Cerami, A., Maillard Reactions in Food, Prog. Food Nutr. Sci. 5, 315, Pergamon Press, London］、血管壁の硬化にも関連があると

考えられている［Rosenburg, H., Modrak, J. B., Hassing, J. M., Al-Turk, W A., & Stohs, S. J., Biochem. Biophys. Res. Commun., 91, 498 (1979)］。また、糖尿病性神経疾患の原因として、神経ミエリンタンパク質の非酵素的グリコシル化が考えられる［Monnier, V. M. et al., Clin. Endocrinol Metab. 11, 431 (1982)］。

【０００９】このように、メイラード反応は糖尿病の種々の合併症だけでなく、加齢（老化）に伴う種々の疾患にも関与しているものと考えられている。また、最近の研究では、蛋白のグリコシル化にフリーラジカルが関与している可能性があることが報告されている［Diabete & Metabolism (Paris), 14, 25-30(1988)］。

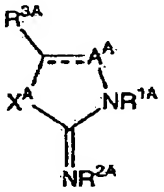
【００１０】

【従来の技術】以上のような背景のもとに、最近メイラード反応を阻害する物質の検索が行なわれている。例えば、ブラウンリーらはアミノグアニジンがインビトロ(in vitro)において、メイラード反応を阻止すること、さらにアミノグアニジンを糖尿病ラットに投与すると動脈壁におけるＡＧＥの生成が抑制されることを示した［Brownlee, M. et al., Science, 232, 1629 (1986)］。そしてその作用メカニズムとして求核性ヒドラジン化合物であるアミノグアニジンのアミノ基（グアニジノ基に結合した）がアマドリ転位生成物中の活性カルボニル基を封鎖し、アマドリ転位生成物がさらに架橋重合されることを阻止するためであるとしている。

【００１１】さらに特開昭６２－１４２１１４号明細書では、アマドリ転位生成物中の活性カルボニル基と反応しうる活性窒素含有基（グアニジノ基に結合したアミノ基）を有する化合物からなる二次グリコシル化最終産物の生成を抑制する組成物が示唆されており、具体的にはアミノグアニジン、α－ヒドラジノヒスチジンおよびリジンが開示されている。

【００１２】また、特開平７－１３３２６４号明細書には、一般式（Ａ）

【化１１】

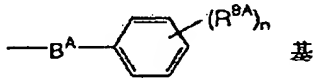


（Ａ）

【００１３】（式中、Ｒ'^は水素原子、低級アルコキシカルボニル低級アルキル基等を表わし、Ｒ^{2A}はアミノ基、置換フェニルスルホニルアミノ基または－Ｎ＝Ｒ^{4A}基(基中、Ｒ^{4A}は低級アルキリデン基、低級シクロアルキリデン基、フェニル低級アルキリデン基等を表わす。）を表わし、Ｒ^{3A}は水素原子、低級アルキル基、低級アルケニル基、フェニル低級アルコキシ低級アルキル基、水酸基を有することのあるフェニル基、５員もしくは６員の不飽和低級ヘテロ環低級アルキル基、－Ｎ（Ｒ^{6A}）Ｒ^{7A}基(基中、Ｒ^{6A}は低級アルキル基、カルボキシ低級アルキル基、低級アルコキシカルボニル低級アルキル基、６－ヒドロキシ－２，５，７，８－テトラメチル－２－クロマニル－メチルオキシ基等を表わし、Ｒ^{7A}は水素原子または低級アルキル基を表わす。）、または

【００１４】

【化１２】



基

（基中、Ｂ^は低級アルキレン基を表わし、Ｒ^{8A}は水酸基、ニトロ基、アミノ基、ハロゲン原子、低級アルキル基、低級アルコキシ基、フェノキシ基、フェニル低級アルキル基、低級アルキルチオ基、フェニル低級アルキルチオ基等を表わし、ｎは０または１～３を表わす。）を表わし、Ｘ^は－Ｓ－または－Ｎ（Ｒ'^{0A}）－（Ｒ'^{0A}は水素原子、または低級アルコキシカルボニル低級アルキル基を表わす。）を表わし、

【００１５】

【化１３】

が単結合を表わす場合は、Ａ^はカルボニル基を表わし、

【化１４】

が二重結合を表わす場合は、Ａ^は＝Ｃ（Ｒ''^）－（Ｒ''^は低級アルキル基、低級アルコキシカルボニル低級アルキル基等を表わす。）を表わす。）で示される化合物がメイラード反応阻害剤として開示されている。

【００１６】

【発明の目的】本発明者らは、メイラード反応に対して優れた抑制作用を有し、かつ安全性の高い新規な化合物を見出すべく研究を行ない、一般式（Ｉ）で示されるグアニジル誘導体が目的を達成することを見出した。また、該誘導体が抗酸化作用をも併せ持つことも見出した。

【００１７】

【従来技術との比較】本発明化合物のグアニジル誘導体は、これまでまったく知られていない新規な化合物である。詳しく説明すると、従来技術中、式（Ａ）で示される化合物はチアゾールまたはイミダゾール環を有する化合物である。しかし、それらの環の２位に置換している基はヒドラジノ（Ｒ^{2A}がアミノ基の場合）または置換ヒドラジノ基（Ｒ^{2A}が置換フェニルスルホニルアミノ基または－Ｎ＝Ｒ^{4A}の場合）である。それに対し、本発明化合物はチアゾール、オキサゾールまたはイミダゾール環の２位にグアニジル基を必須とする化合物である。よって、本発明化合物は式（Ａ）で示される化合物とは、全く異なる構造を有する化合物であると言える。また、本発明化合物は、抗酸化作用を併せ持つ点からも、前記式

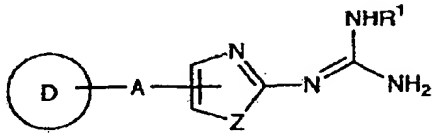
（Ａ）で示される化合物とは異なると言える。

【００１８】

【発明の開示】本発明は

１）一般式（Ｉ）

【化１５】

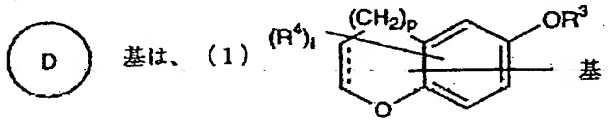


(I)

【００１９】（式中、Ｚは硫黄原子、酸素原子またはＮＲ^{2}（基中、Ｒ^{2}は水素原子またはＣ１～４のアルキル基を表わす。）を表わし、Ｒ^{1}は水素原子、Ｃ１～４のアルキル基またはＣ２～５のアシル基を表わし、Ａは単結合、Ｃ１～８のアルキレン基、１個の炭素原子が１個の硫黄原子または酸素原子に置き換わっているＣ２～８のアルキレン基を表わし、

【００２０】

【化１６】

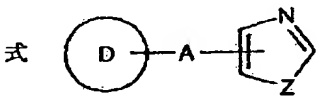


基は、（１）

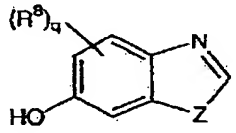
基

（基中、Ｒ^{3}は水素原子、Ｃ１～４のアルキル基またはＣ２～５のアシル基を表わし、ｌは０または１～１０を表わし、Ｒ^{4}はＣ１～４のアルキル基を表わし、ｐは０または１～２を表わす。）、

【００２１】



式　　は、式



（式中、Ｒ^{5}はＣ１～７のアルキル基、フェニル基またはフェニルーＣ１～４アルキル基、Ｃ５～７のシクロアルキル基またはＣ５～７のシクロアルキルーＣ１～４アルキル基を表わし、ｑは０または１～３を表わす。）を表わす。

【００２４】ただし、（ｉ）Ａ中、硫黄原子または酸素原子が

【化２０】

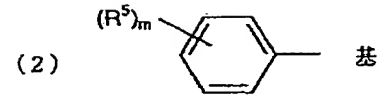
に直接、結合することはなく、（ii）

【化２１】

が（１）の場合、Ａ中、硫黄原子または酸素原子が

【化２２】

【化１７】

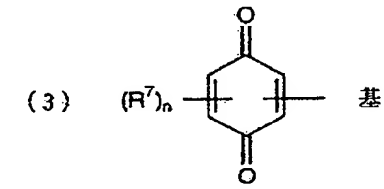


（２）　　基

（基中、Ｒ^{6}はＣ１～７のアルキル基、ＯＲ^{6}基（基中、Ｒ^{6}は水素原子、Ｃ１～４のアルキル基、Ｃ２～５のアシル基、フェニル基またはフェニルーＣ１～４アルキル基を表わす。）、ハロゲン原子、フェニル基またはフェニルーＣ１～４アルキル基、Ｃ５～７のシクロアルキル基またはＣ５～７のシクロアルキルーＣ１～４アルキル基を表わし、ｍは０または１～５を表わす。）またはベンゼン環が縮合している上記の環、または

【００２２】

【化１８】



（３）　　基

（基中、Ｒ^{7}はＣ１～７のアルキル基、フェニル基またはフェニルーＣ１～４アルキル基、Ｃ５～７のシクロアルキル基またはＣ５～７のシクロアルキルーＣ１～４アルキル基を表わし、ｎは０または１～３を表わす。）を表わす。

【００２３】また、

【化１９】

に直接、結合することはない。）で示されるグアニジル誘導体、それらの酸付加塩、

２）それらの製造方法、および

３）それらを有効成分として含有する薬剤に関する。

【００２５】一般式（Ｉ）中、Ｒ^{1}、Ｒ^{2}、Ｒ^{3}、Ｒ^{4}およびＲ^{6}で示されるＣ１～４のアルキル基とは、メチル、エチル、プロピル、ブチル基およびこれらの異性体基である。一般式（Ｉ）中、Ｒ^{1}、Ｒ^{3}およびＲ^{6}で示されるＣ２～５のアシル基とは、アセチル、プロピオニル、ブチリル、バレリル基およびこれらの異性体基である。一般式（Ｉ）中、Ｒ^{5}、Ｒ^{6}、Ｒ^{7}およびＲ^{8}で示されるフェニルーＣ１～４アルキル基とは、フェニル基１個によって置換されたメチル、エチル、プロピル、ブチル基およびこれらの異性体基である。一般式（Ｉ）中、Ｒ^{5}、Ｒ^{7}およびＲ^{8}で示されるＣ１～７のアルキル基とは、メチ

ル、エチル、プロピル、ブチル、ペンチル、ヘキシル、ヘプチル基およびそれらの異性体基である。

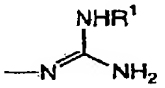
【００２６】一般式（Ｉ）中、Ａで示されるＣ１～８のアルキレン基とはメチレン、エチレン、トリメチレン、テトラメチレン、ペンタメチレン、ヘキサメチレン、ヘプタメチレン、オクタメチレン基およびこれらの異性体基である。一般式（Ｉ）中、Ａで示される１個の炭素原子が１個の硫黄原子または酸素原子に置き換わったＣ２～８のアルキレン基とはエチレン、トリメチレン、テトラメチレン、ペンタメチレン、ヘキサメチレン、ヘプタメチレン、オクタメチレン基およびこれらの異性体基中の炭素原子１個が硫黄原子または酸素原子１個と置き換わったものである。一般式（Ｉ）中、R^5で示されるハロゲン原子としては、フッ素、塩素、臭素およびヨウ素が挙げられる。

【００２７】本発明においては、明細書中および構造式

において特に指示しない限り異性体はこれをすべて包含する。例えば、アルキル基、アルキレン基およびアルケニレン基には直鎖のもの、分枝鎖のものが含まれ、アルケニレン基中の二重結合中の二重結合は、Ｅ、ＺおよびＥＺ混合物であるものを含む。また、分枝鎖のアルキル基が存在する場合等の不斉炭素原子の存在により生ずる異性体も含まれる。

【００２８】また本発明中、

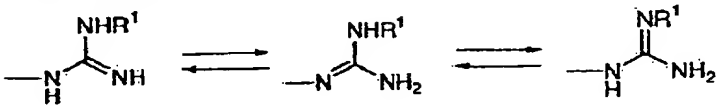
【化２３】



で示される基は、下記に示すように互変異性が存在する。

【００２９】

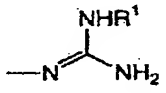
【化２４】



a　　b　　c

【００３０】よって、

【化２５】



で示される基は、上記のａ、ｂおよびｃのすべての基を表わす。

【００３１】

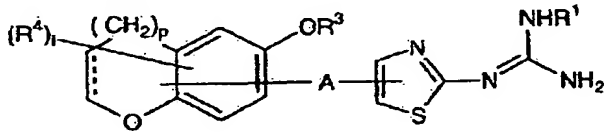
【塩】一般式（Ｉ）で示される化合物は、所望により公知の方法で酸付加塩に変換される。酸付加塩は非毒性かつ水溶性であることが好ましい。適当な酸付加塩としては、例えば塩酸塩、臭化水素酸塩、ヨウ化水素酸塩、硫酸塩、リン酸塩、硝酸塩のような無機酸塩、または酢酸塩、乳酸塩、酒石酸塩、安息香酸塩、クエン酸塩、メタンスルホン酸塩、エタンスルホン酸塩、ベンゼンスルホン酸塩、トルエンスルホン酸塩、イセチオン酸塩、グルクロン酸塩、グルコン酸塩のような有機酸塩が挙げられる。酸付加塩は、一般式（Ｉ）で示される化合物を公知の方法、例えば適当な溶媒中で所望の酸と理論量ずつ反応させることにより得られる。

【００３２】

【本発明の具体的な化合物】本発明の好ましい化合物としては、以下の一般式（Ｉ－Ａ１）、（Ｉ－Ａ２）、（Ｉ－Ａ３）、（Ｉ－Ａ４）、（Ｉ－Ｂ１）、（Ｉ－Ｂ２）、（Ｉ－Ｂ３）、（Ｉ－Ｂ４）、（Ｉ－Ｃ１）、（Ｉ－Ｃ２）、（Ｉ－Ｃ３）、または（Ｉ－Ｃ４）で示される化合物および実施例の化合物が挙げられる。

【００３３】

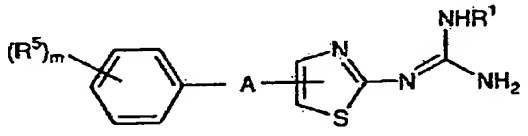
【化２６】



(I-A1)

【００３４】

※　※【化２７】

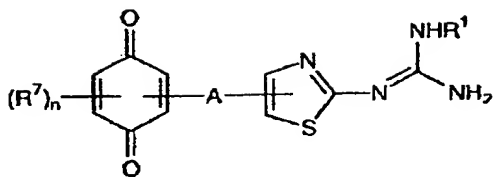


(I-A2)

【００３５】

【化２８】

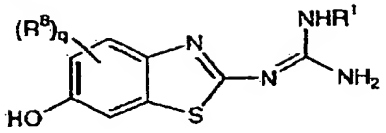
11　　12



(I-A3)

【００３６】

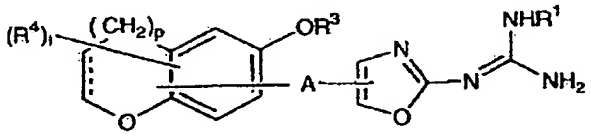
【化２９】



(I-A4)

＊【００３７】

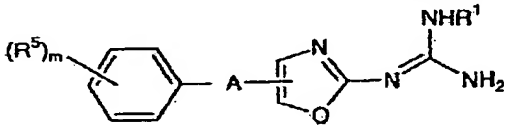
【化３０】



(I-B1)

【００３８】

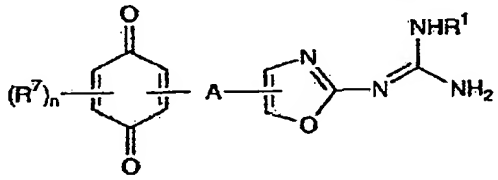
※ ※【化３１】



(I-B2)

【００３９】

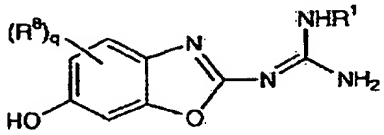
★ ★【化３２】



(I-B3)

【００４０】

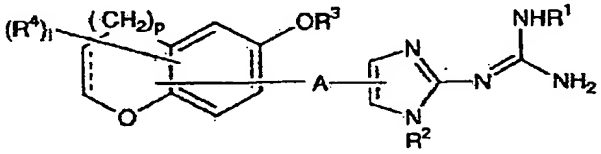
【化３３】



(I-B4)

【００４１】

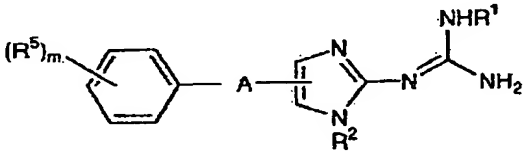
【化３４】



(I-C1)

【００４２】

◆ ◆【化３５】

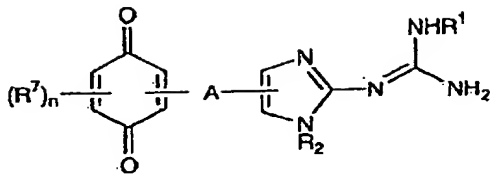


(I-C2)

【００４３】

【化３６】

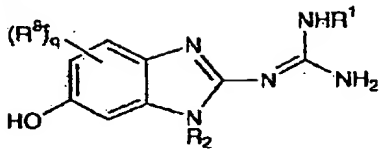
13　　14



(I-C3)

【００４４】

【化３７】



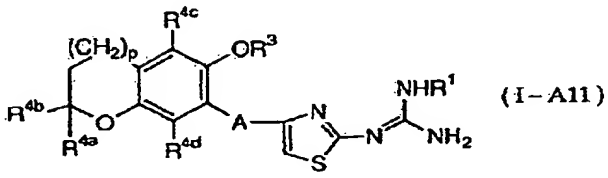
(I-C4)

＊【００４５】具体的な化合物としては、以下の表１～２４で示される化合物および実施例の化合物が挙げられる。なお、表中、Ｍｅはメチル基を表わし、ｔ－Ｂｕはターシャリーブチル基を表わし、Ｐｈはフェニル基を表わし、Ｂｚはベンジル基を表わす。

【００４６】

＊　【表１】

表１

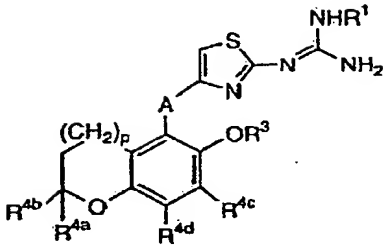


(I-A11)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

【００４７】　　【表２】

表２



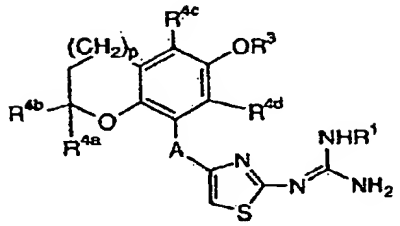
(I－A12)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

【００４８】

【表３】

表3



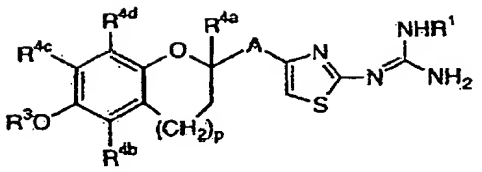
(I－A13)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

【0049】

【表4】

表４



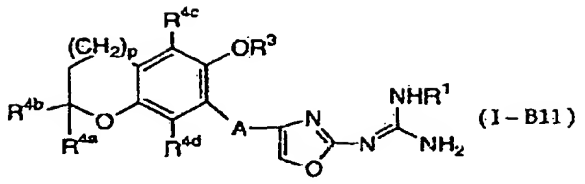
(I－A14)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

【００５０】

【表５】

表5



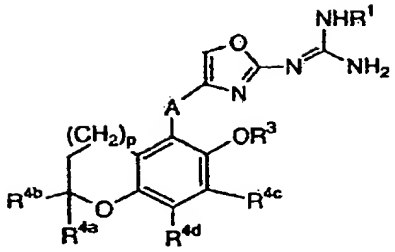
(I-B11)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$(CH_2)_4$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

【0051】

【表6】

表6



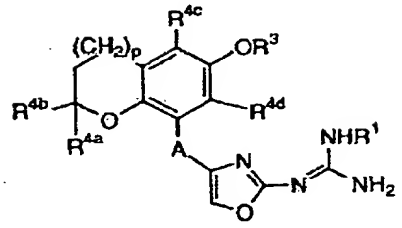
(I－B12)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

【0052】

【表7】

表７



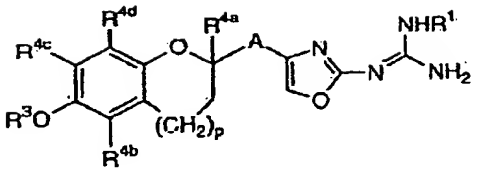
(I－B13)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

【００５３】

【表８】

表８



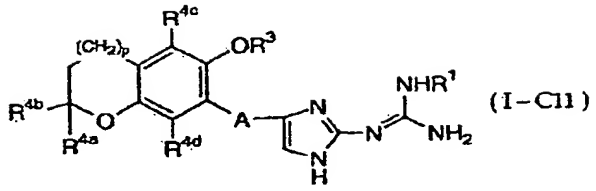
(I－B14)

	R¹	p	R⁴ᵃ	R⁴ᵇ	R⁴ᶜ	R⁴ᵈ	R³	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

【００５４】

【表９】

表9



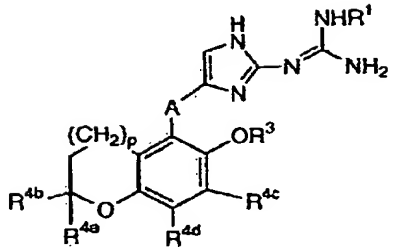
(I-C11)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

【0055】

【表10】

表１０



(I-C12)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

【００５６】

【表１１】

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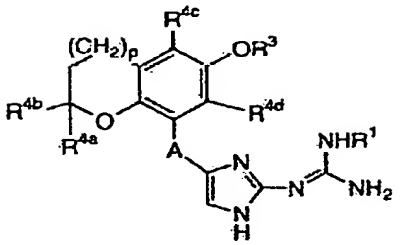
表１１



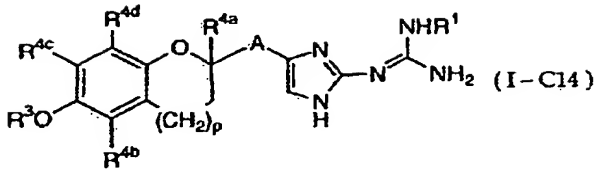
(I－C13)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

【００５７】

【表１２】

表１２



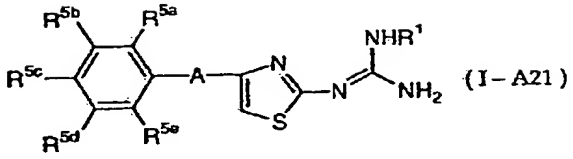
(I-C14)

	R^1	p	R^{4a}	R^{4b}	R^{4c}	R^{4d}	R^3	A
1	H	1	Me	Me	Me	Me	H	単結合
2	H	1	Me	Me	Me	Me	H	$-(CH_2)_2-$
3	H	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
4	H	1	Me	Me	Me	Me	Me	$-(CH_2)_4-$
5	Me	1	Me	Me	Me	Me	H	$-(CH_2)_4-$
6	H	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
7	Me	1	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
8	H	1	Me	Me	Me	Me	H	$-(CH_2)_3SCH_2-$
9	H	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
10	Me	1	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
11	H	1	Me	Me	Me	Me	H	$-(CH_2)_3OCH_2-$
12	H	2	Me	Me	Me	Me	H	$-(CH_2)_2-$
13	H	2	Me	Me	Me	Me	H	$-(CH_2)_4-$
14	H	2	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
15	H	2	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$
16	H	3	Me	Me	Me	Me	H	$-(CH_2)_2-$
17	H	3	Me	Me	Me	Me	H	$-(CH_2)_4-$
18	H	3	Me	Me	Me	Me	H	$-CH_2S(CH_2)_3-$
19	H	3	Me	Me	Me	Me	H	$-CH_2O(CH_2)_3-$

【００５８】

【表１３】

表13



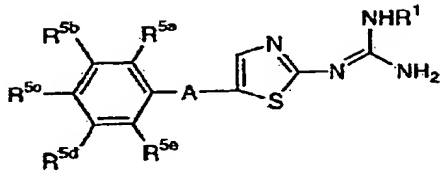
(I－A21)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t−Bu	OH	t−Bu	H	$-(CH_2)_2-$
2	H	H	t−Bu	OMe	t−Bu	H	$-(CH_2)_2-$
3	H	H	t−Bu	H	t−Bu	H	$-(CH_2)_2-$
4	H	H	H	t−Bu	H	H	$-(CH_2)_2-$
5	H	H	t−Bu	OH	t−Bu	H	$-(CH_2)_4-$
6	H	H	t−Bu	OMe	t−Bu	H	$-(CH_2)_4-$
7	H	H	t−Bu	H	t−Bu	H	$-(CH_2)_4-$
8	Me	H	t−Bu	OH	t−Bu	H	$-(CH_2)_4-$
9	Me	H	t−Bu	OMe	t−Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t−Bu	OH	t−Bu	H	$-S(CH_2)_2-$
17	H	H	t−Bu	OMe	t−Bu	H	$-S(CH_2)_2-$
18	H	H	t−Bu	H	t−Bu	H	$-S(CH_2)_4-$
19	H	H	t−Bu	OH	t−Bu	H	$-S(CH_2)_4-$
20	H	H	t−Bu	H	t−Bu	H	$-O(CH_2)_4-$

【0059】

30　【表14】

表１４



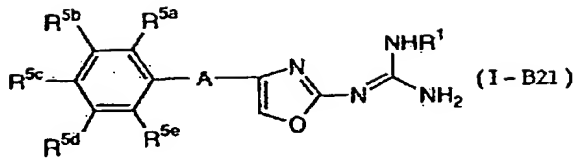
(I－A22)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_2-$
2	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_2-$
3	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_2-$
4	H	H	H	t－Bu	H	H	$-(CH_2)_2-$
5	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
6	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
7	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_4-$
8	Me	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
9	Me	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_2-$
17	H	H	t－Bu	OMe	t－Bu	H	$-S(CH_2)_2-$
18	H	H	t－Bu	H	t－Bu	H	$-S(CH_2)_4-$
19	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_4-$
20	H	H	t－Bu	H	t－Bu	H	$-O(CH_2)_4-$

【００６０】

30　【表１５】

表１５



(I－B21)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_2-$
2	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_2-$
3	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_2-$
4	H	H	H	t－Bu	H	H	$-(CH_2)_2-$
5	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
6	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
7	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_4-$
8	Me	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
9	Me	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_2-$
17	H	H	t－Bu	OMe	t－Bu	H	$-S(CH_2)_2-$
18	H	H	t－Bu	H	t－Bu	H	$S(CH_2)_4$
19	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_4-$
20	H	H	t－Bu	H	t－Bu	H	$-O(CH_2)_4-$

【００６１】

30　【表１６】

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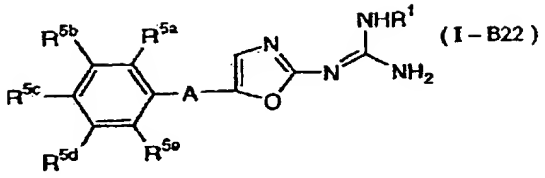
表１６

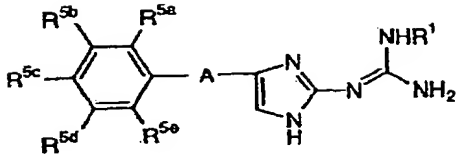


(I－B22)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_2-$
2	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_2-$
3	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_2-$
4	H	H	H	t－Bu	H	H	$-(CH_2)_2-$
5	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
6	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
7	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_4-$
8	Me	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
9	Me	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_2-$
17	H	H	t－Bu	OMe	t－Bu	H	$-S(CH_2)_2-$
18	H	H	t Bu	H	t－Bu	H	$-S(CH_2)_4-$
19	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_4-$
20	H	H	t－Bu	H	t－Bu	H	$-O(CH_2)_4-$

【００６２】　　30　【表１７】

表１７

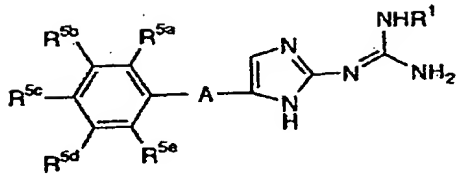


(I－C21)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_2-$
2	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_2-$
3	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_2-$
4	H	H	H	t－Bu	H	H	$-(CH_2)_2-$
5	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
6	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
7	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_4-$
8	Me	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
9	Me	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_2-$
17	H	H	t－Bu	OMe	t－Bu	H	$-S(CH_2)_2-$
18	H	H	t－Bu	H	t－Bu	H	$-S(CH_2)_4-$
19	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_4-$
20	H	H	t－Bu	H	t－Bu	H	$-O(CH_2)_4-$

【００６３】　　30　【表１８】

表１８

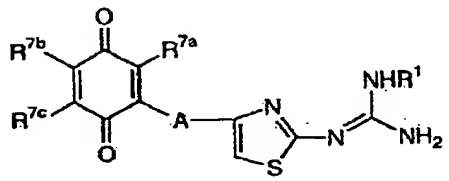


(I－C22)

	R^1	R^{5a}	R^{5b}	R^{5c}	R^{5d}	R^{5e}	A
1	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_2-$
2	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_2-$
3	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_2-$
4	H	H	H	t－Bu	H	H	$-(CH_2)_2-$
5	H	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
6	H	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
7	H	H	t－Bu	H	t－Bu	H	$-(CH_2)_4-$
8	Me	H	t－Bu	OH	t－Bu	H	$-(CH_2)_4-$
9	Me	H	t－Bu	OMe	t－Bu	H	$-(CH_2)_4-$
10	H	OH	H	H	H	H	単結合
11	H	H	H	OH	OH	H	単結合
12	H	OH	Cl	OMe	H	OMe	単結合
13	H	H	H	OPh	H	H	単結合
14	H	H	Ph	H	H	H	単結合
15	H	H	H	Bz	H	H	単結合
16	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_2-$
17	H	H	t－Bu	OMe	t－Bu	H	$-S(CH_2)_2-$
18	H	H	t－Bu	H	t－Bu	H	$-S(CH_2)_4$
19	H	H	t－Bu	OH	t－Bu	H	$-S(CH_2)_4-$
20	H	H	t－Bu	H	t－Bu	H	$-O(CH_2)_4-$

【００６４】
【表１９】

表１９

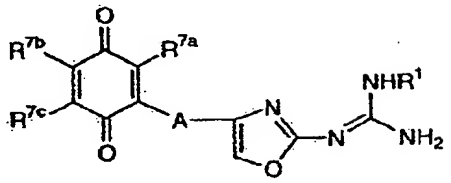


(I－A31)

	R^1	R^{7a}	R^{7b}	R^{7c}	A
1	H	Me	Me	Me	$-(CH_2)_2-$
2	Me	Me	Me	Me	$-(CH_2)_2-$
3	H	Me	Me	Me	$-(CH_2)_4-$
4	H	Me	Me	Me	$-S(CH_2)_4-$
5	H	Me	Me	Me	$-O(CH_2)_4-$

【００６５】
【表２０】

表２０



(I－B31)

	R^1	R^{7a}	R^{7b}	R^{7c}	A
1	H	Me	Me	Me	$-(CH_2)_2-$
2	Me	Me	Me	Me	$-(CH_2)_2-$
3	H	Me	Me	Me	$-(CH_2)_4-$
4	H	Me	Me	Me	$-S(CH_2)_4-$
5	H	Me	Me	Me	$-O(CH_2)_4-$

【００６６】
【表２１】

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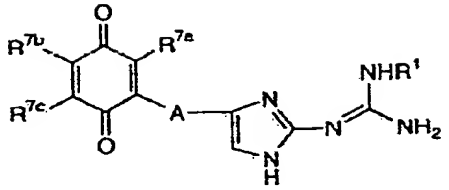
表２１

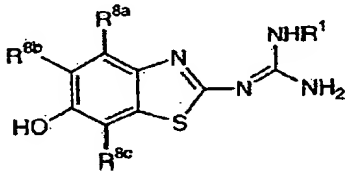


(I-C31)

	R^1	R^{7a}	R^{7b}	R^{7c}	A
1	H	Me	Me	Me	$-(CH_2)_2-$
2	Me	Me	Me	Me	$-(CH_2)_2-$
3	H	Me	Me	Me	$-(CH_2)_4-$
4	H	Me	Me	Me	$-S(CH_2)_4-$
5	H	Me	Me	Me	$-O(CH_2)_4-$

【００６７】
【表２２】

表２２

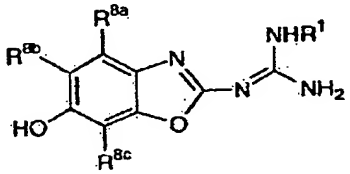


(I-A41)

	R^1	R^{8a}	R^{8b}	R^{8c}
1	H	Me	Me	Me
2	Me	Me	Me	Me
3	H	Me	t-Bu	t-Bu
4	H	Me	Ph	Me
5	H	Me	Bz	Me

【００６８】
【表２３】

表２３



(I-B41)

	R^1	R^{8a}	R^{8b}	R^{8c}
1	H	Me	Me	Me
2	Me	Me	Me	Me
3	H	Me	t-Bu	t-Bu
4	H	Me	Ph	Me
5	H	Me	Bz	Me

【００６９】
【表２４】

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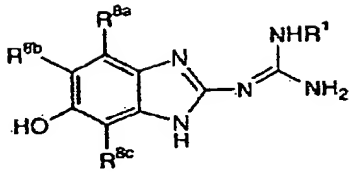
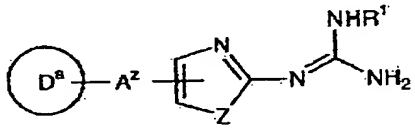
表２４



(I-C41)

	R^1	R^{8a}	R^{8b}	R^{8c}
1	H	Me	Me	Me
2	Me	Me	Me	Me
3	H	Me	t-Bu	t-Bu
4	H	Me	Ph	Me
5	H	Me	Bz	Me

【００７０】
【本発明化合物の製造方法】一般式（Ｉ）で示される本発明化合物中、（１）一般式（ＩＡ）
【化３８】



(IA)

【００７１】［式中、
【化３９】

は
【化４０】

と同じ意味を表わすが、
【化４１】

中のR^3がＣ１～４のアルキル基、Ｃ２～５のアシル基または酸で除去できる基（例えば、Ｃ２～４のアルコキシアルキル基）を表わし、R^6がＣ１～４のアルキル基、Ｃ２～５のアシル基、フェニル基、フェニル－Ｃ１～４アルキル基または酸で除去できる基（例えば、Ｃ２～４のアルコキシアルキル基）を表わすものとし、A^zはＡと同じ意味を表わすが、硫黄原子がアルキレンを介して
【化４２】

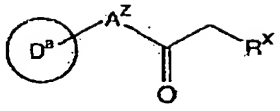
に結合している場合を除くものとし、その他の記号は前記と同じ意味を表わす。］で示される化合物は、一般式

51

(IIa)

【００７２】

【化４３】

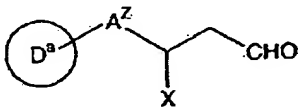


(IIa)

(式中、R^xはハロゲン原子またはアセチルオキシ基を表わし、その他の記号は前記と同じ意味を表わす。)または一般式(IIb)

【００７３】

【化４４】

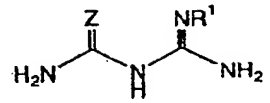


(IIb)

(式中、Xはハロゲン原子を表わし、その他の記号は前記と同じ意味を表す。)で示される化合物と一般式(IIIa)

52

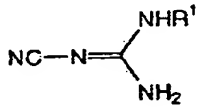
【化４５】



(IIIa)

(すべての記号は前記と同じ意味を表わす。)で示される化合物または一般式(IIIb)

【化４６】

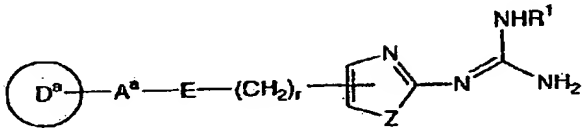


(IIIb)

(すべての記号は前記と同じ意味を表わす。)で示される化合物と反応させるか、あるいはR^3またはR^6が酸で除去できる基である場合は、引き続いて酸処理を行なうことによって製造することができる。

【００７４】また、(2)一般式(I)で示される本発明化合物中、一般式(IB)

【化４７】

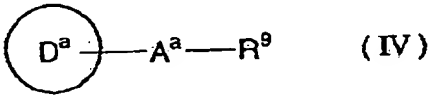


(IB)

【００７５】(式中、A^aはＣ１～６のアルキレン基を表わし、Eは硫黄原子または酸素原子を表わし、rは１～６の整数を表わし、その他の記号は前記と同じ意味を表わす。ただし、A^aと$(CH_2)_r$との炭素原子の合計数は７以下である。)で示される化合物は、一般式(IV)

【００７６】

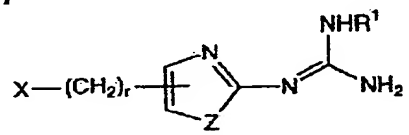
【化４８】



(IV)

(式中、R^9は水酸基またはアセチルチオ基を表わし、その他の記号は前記と同じ意味を表わす。)で示される化合物と、一般式(V)

【化４９】



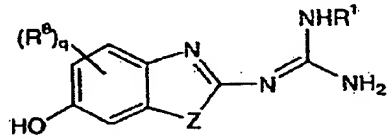
(式中、すべての記号は前記と同じ意味を表わす。)で示される化合物と反応させるか、あるいは

【化５０】

中のR^3またはR^6が酸で除去できる基である場合は、引き続いて酸処理を行なうことによって製造することができる。

【００７７】また、(3)一般式(I)で示される本発明化合物中、一般式(IC)

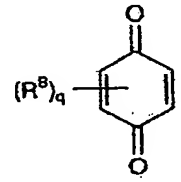
【化５１】



(IC)

(式中、すべての記号は前記と同じ意味を表わす。)で示される化合物は、一般式(VI)

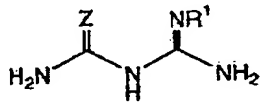
【化５２】



(VI)

(式中、すべての記号は前記と同じ意味を表わす。)で示される化合物と、一般式(IIIa)

【化５３】



(IIIa)

(すべての記号は前記と同じ意味を表わす。)で示される化合物と反応させることによって製造することができ

る。

【００７８】一般式（ＩＩａ）または（ＩＩｂ）と一般式（ＩＩＩａ）との反応は公知であり、例えば、アルコール性溶媒（メタノール、エタノール等）中、８０～１２０℃の温度で反応させることにより行なわれる。一般式（ＩＩａ）または（ＩＩｂ）と一般式（ＩＩＩｂ）との反応は公知であり、例えば、アルコール性溶媒（メタノール、エタノール等）中、酸(塩酸等）存在下、１０～４０℃で反応させることにより行なわれる。酸による処理は、アルコール性溶媒（メタノール、エタノール等）中、有機酸（酢酸、トリフルオロ酢酸等）もしくは無機酸（塩酸、硫酸等）存在下で反応させることによって行なわれる。一般式（ＩＶ）と一般式（Ｖ）との反応は公知であ＊

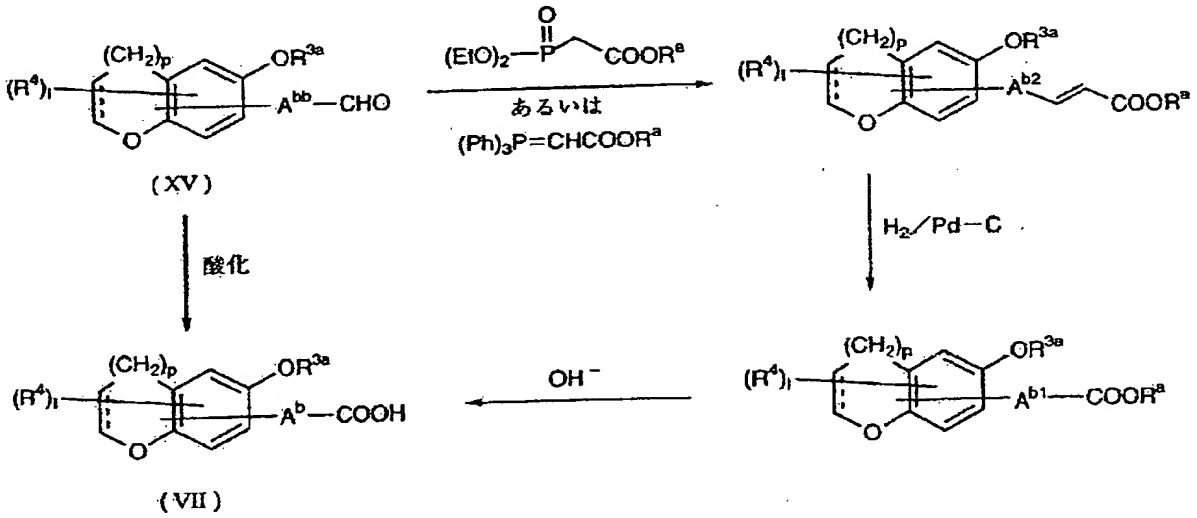
＊り、例えば、アルコール性溶媒（メタノール、エタノール等）中、塩基（ナトリウムエトキシド等）存在下で反応させることによって行なわれる。一般式（ＶＩ）と一般式（ＩＩＩａ）との反応は公知であり、例えば、アルコール性溶媒（メタノール、エタノール等）中、酸（塩酸等）存在下で反応させることによって行なわれる。

【００７９】出発原料として用いた一般式（ＩＩａ）、（ＩＩｂ）および（ＩＶ）で示される化合物は、反応工程式１～８に示した方法、または公知の方法、例えば、本明細書記載の方法により製造することができる。

【００８０】

【化５４】

反応工程式１

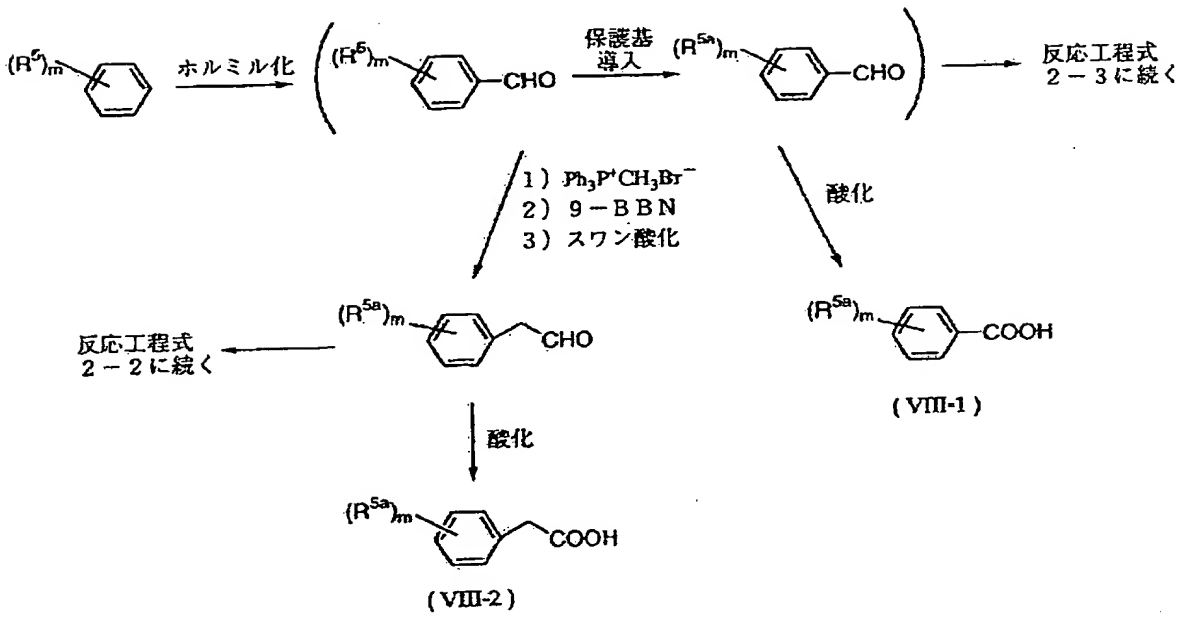


【００８１】

【化５５】

55　　56

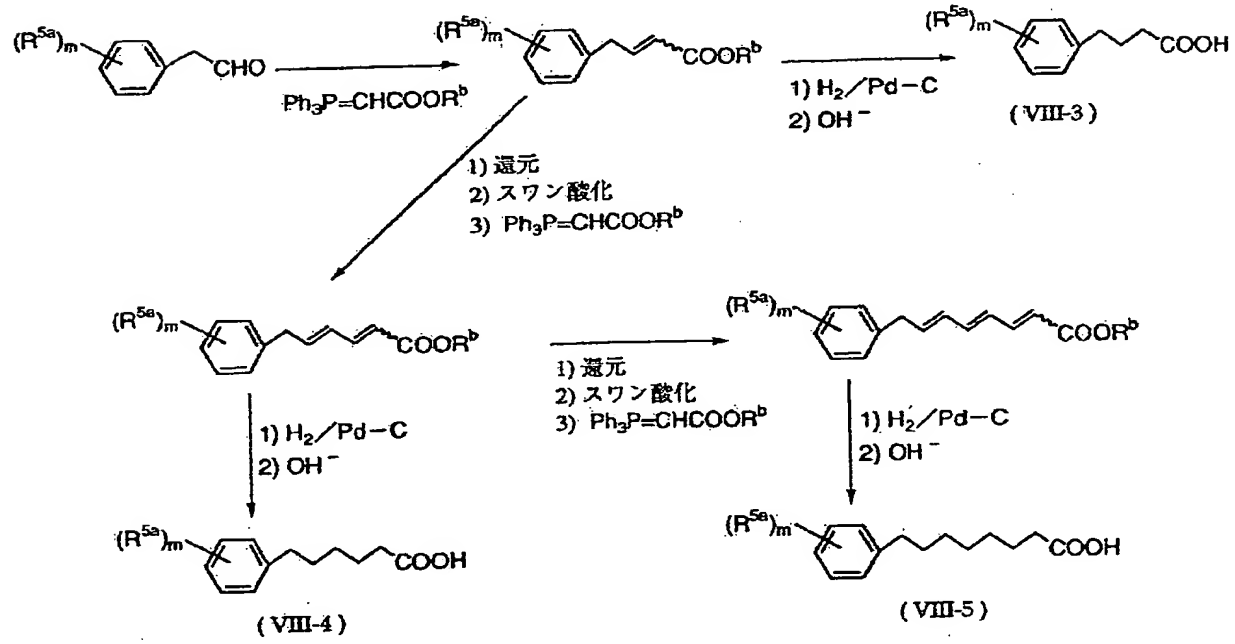
反応工程式２－１



【００８２】

＊　＊【化５６】

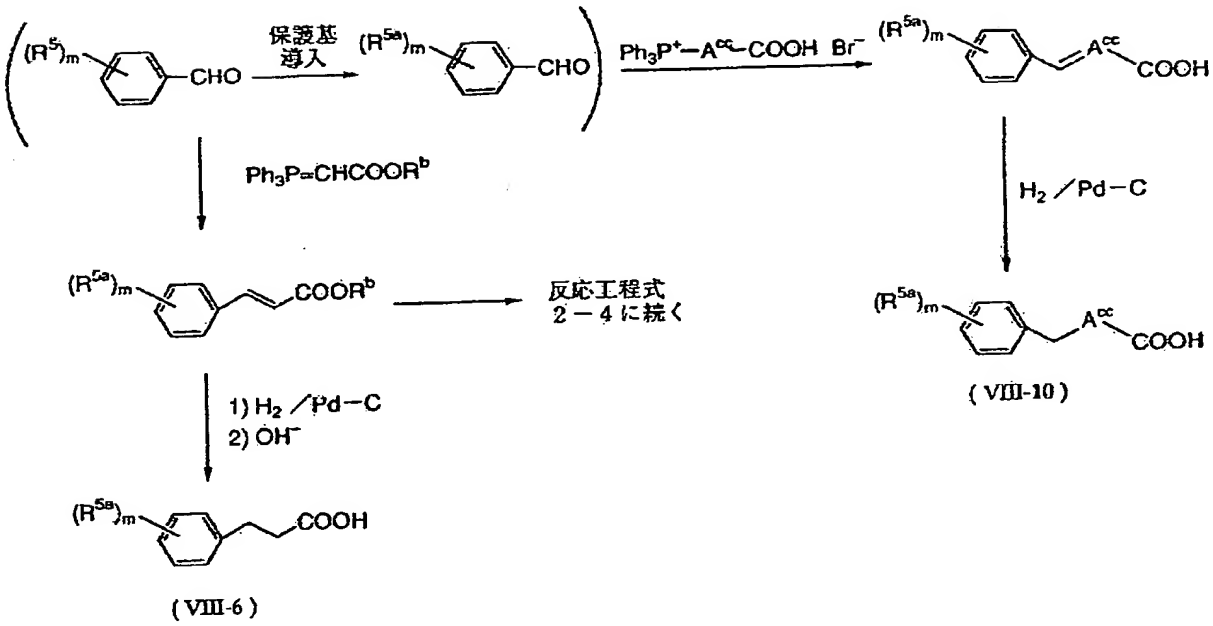
反応工程式２－２



【００８３】

【化５７】

反応工程式２－３

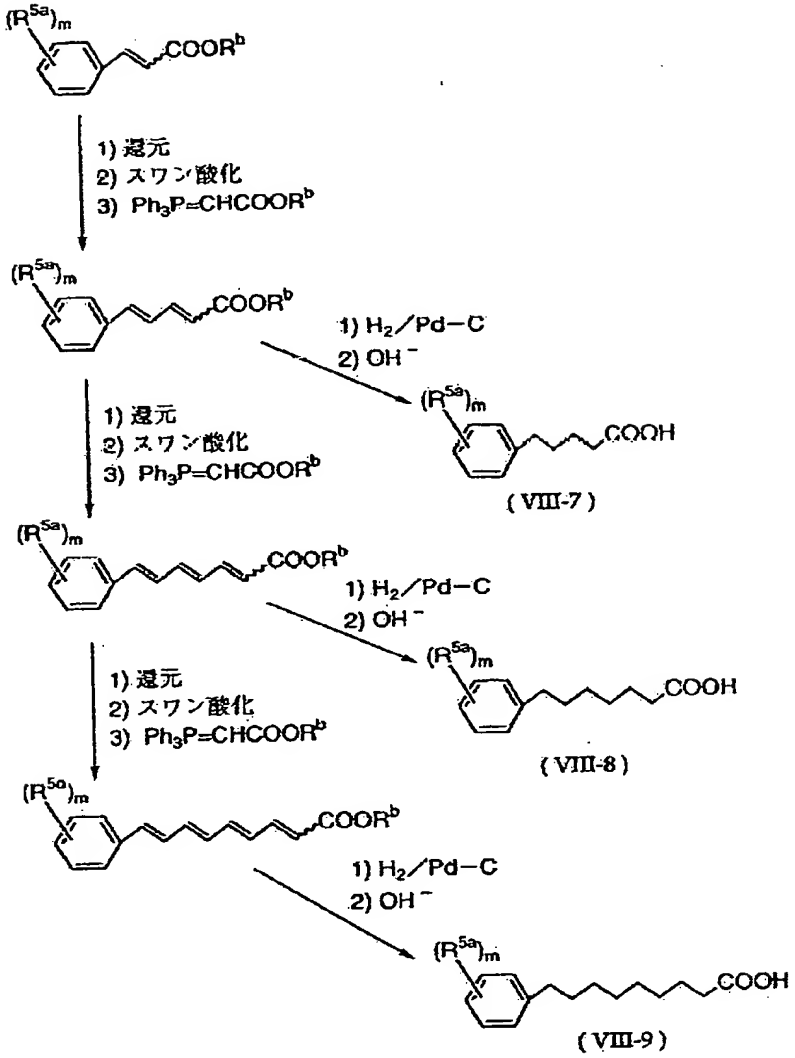


【００８４】

【化５８】

59　　60

反応工程式２－４

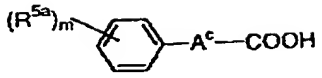


【化５９】

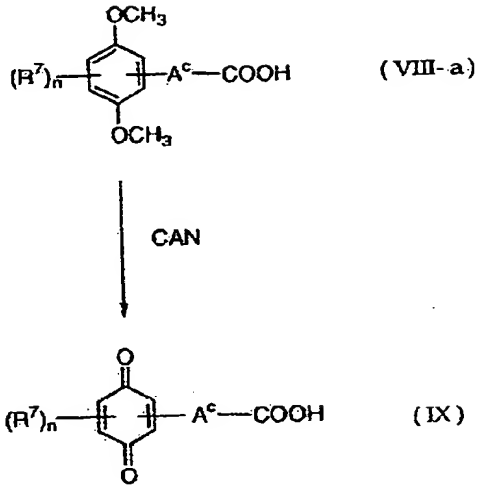
【００８５】

61　　62

反応工程式３



（ＶＩＩＩ）＝（ＶＩＩＩ-1~10）



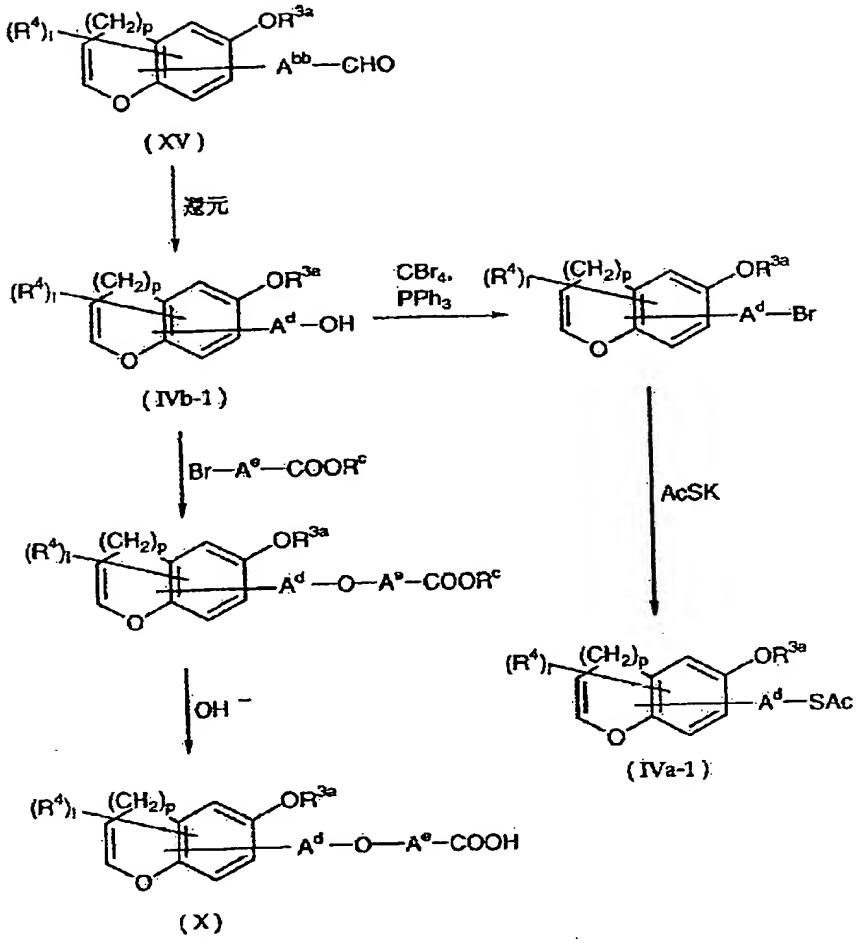
（ＶＩＩＩ-ａ）　　（ＩＸ）

【化６０】

【００８６】

63　　64

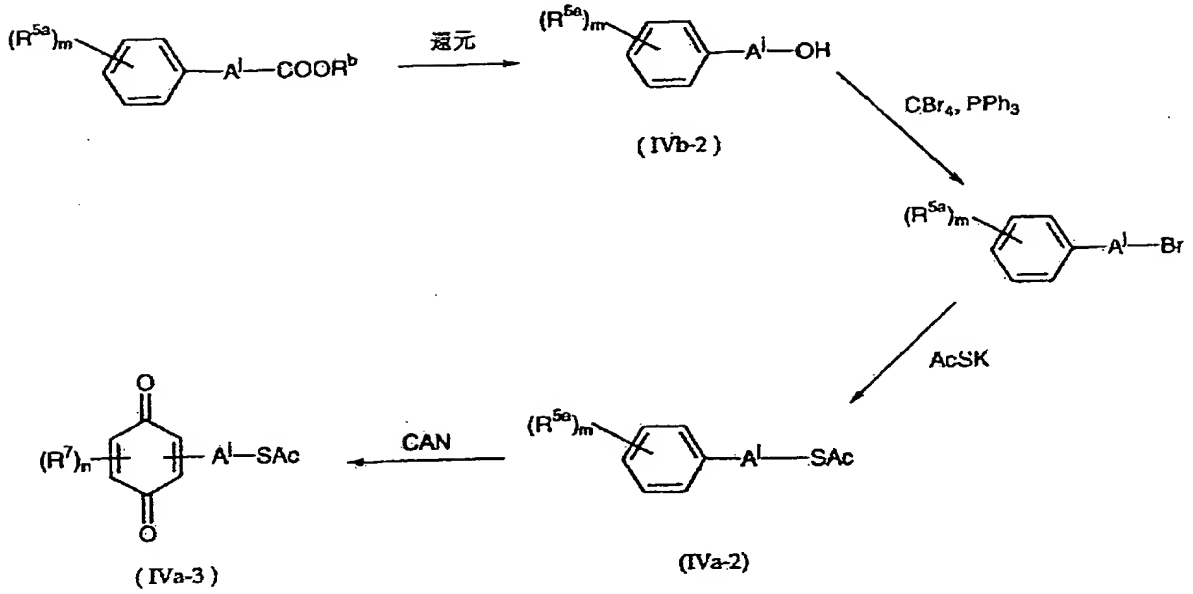
反応工程式４



【化６１】

【００８７】

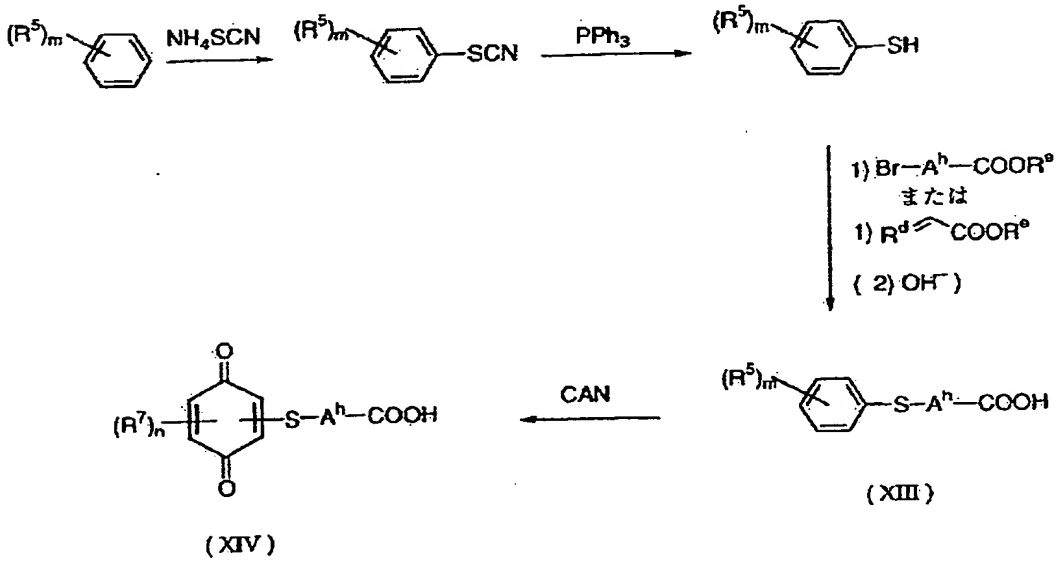
反応工程式５



【００８８】

＊　＊【化６２】

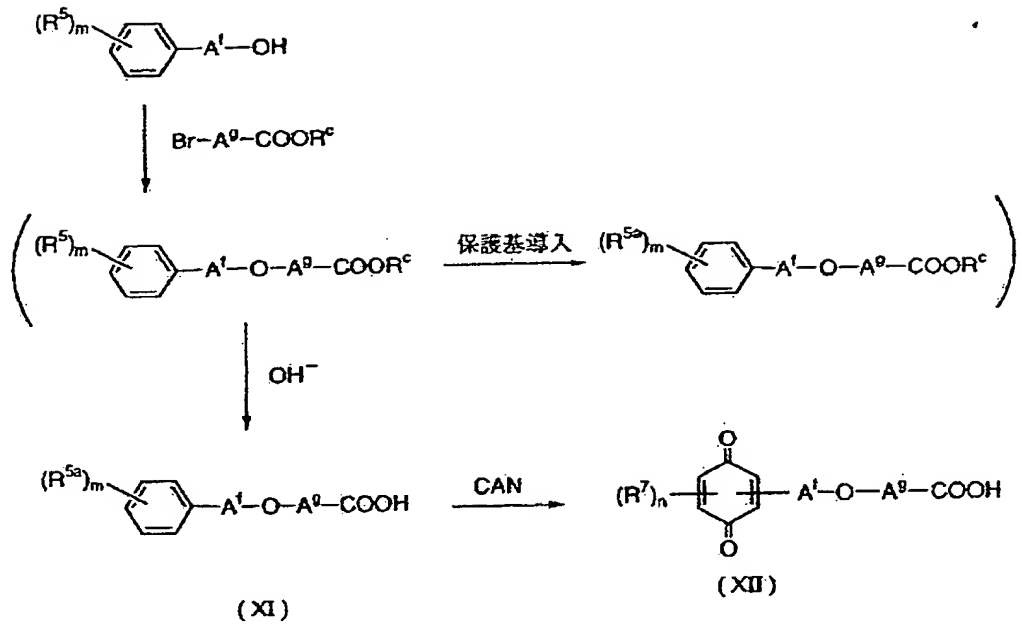
反応工程式６



【００８９】

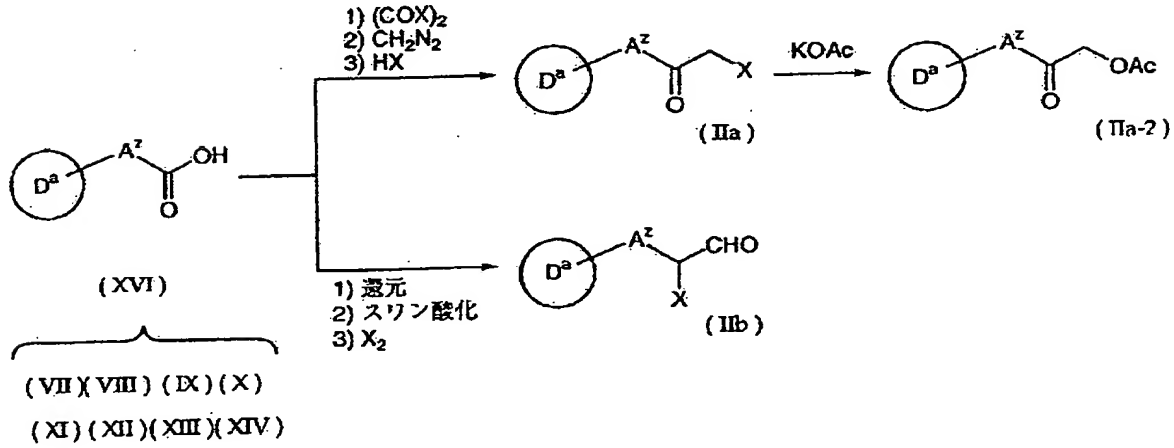
【化６３】

反応工程式７



【００９０】　　＊　＊【化６４】

反応工程式８



【００９１】反応工程式中、A^{b}は、単結合またはＣ１～８のアルキレン基を表わし、A^{b1}は、Ｃ７または８のアルキレン基を表わし、A^{b2}は、Ｃ５または６のアルキレン基を表わし、A^{bb}は、単結合またはＣ１～６のアルキレン基を表わし、A^{c}は、単結合またはＣ１～８のアルキレン基を表わし、A^{c1}は、Ｃ１～７のアルキレン基を表わし、A^{c2}は、Ｃ２～８のアルキレン基を表わし、A^{d}は、Ｃ１～６のアルキレン基を表わし、A^{e}は、Ｃ１～６のアルキレン基（ただし、A^{d}とA^{e}の炭素の合計数は７以下である。）を表わし、A^{f}は、単結合またはＣ１～６のアルキレン基を表わし、A^{g}は、Ｃ１～７のアルキレン基（ただし、A^{f}とA^{g}の炭素の合計数は７以下である。）を表わし、A^{h}は、Ｃ１～７のアルキレン基を表わし、A^{i}は、Ｃ１～６のアルキレン基を表わし、A^{j}は、Ｃ２～８のアルケニレン基を表わし、

【００９２】R^{3a}は、Ｃ１～４のアルキル基またはＣ２～５のアシル基または酸で除去できる基（例えば、Ｃ２～４のアルコキシアルキル基）を表わし、R^{6a}はＣ１～７のアルキル基、OR^{6a}基（基中、R^{6a}はＣ１～４のアルキル基、Ｃ２～５のアシル基、酸で除去できる基（例えば、Ｃ２～４のアルコキシアルキル基）、フェニル基またはフェニル－Ｃ１～４アルキル基を表わす。）、ハ

ロゲン原子、フェニル基またはフェニルーＣ１～４アルキル基を表わし、Ｒᵇは、Ｃ１～４のアルキル基を表わし、Ｒᶜは、Ｃ１～４のアルキル基を表わし、Ｒᵈは、水素原子またはＣ１～５のアルキル基を表わし、Ｒᵉは、水素原子またはＣ１～４のアルキル基を表わし、Ｐｈは、フェニル基を表わし、Ｅｔは、エチル基を表わし、ＡｃＳＫは、チオ酢酸カリウムを表わし、ＣＡＮは、セリウムアンモニウムニトレートを表わし、９－ＢＢＮは、９－ボラビシクロ［３．３．１］ノナンを表わす。

【００９３】本発明におけるその他の出発物質および各試薬は、それ自体公知であるか、または公知の方法により製造することができる。例えば、一般式（Ｖ）で示される化合物の製造方法は、特開昭５３－１４７０６９号明細書に開示されている。また、一般式（XV）で示される化合物はＰＣＴ出願番号ＪＰ９５／２９４号明細書に開示されている。

【００９４】反応生成物は、通常の精製手段、例えば常圧下または減圧下における蒸留、シリカゲルまたはケイ酸マグネシウムを用いた高速液体クロマトグラフィー、薄層クロマトグラフィー、あるいはカラムクロマトグラフィーまたは洗浄、再結晶等の方法により精製することができる。精製は各反応ごとに行なってもよいし、いくつかの反応終了後行なってもよい。

【００９５】

【発明の効果】本発明化合物のメイラード反応阻害作用は種々のタンパク質と種々の糖を用いるスクリーニング系により確認された。例えば、以下に述べるスクリーニング系により確認された。

(1) 実験方法

リゾチームとフルクトースを0.2Mリン酸ナトリウム緩衝液（ｐＨ 7.4）にそれぞれ１０ｍｇ／ｍｌ，１００ｍＭの濃度となるように溶解し、３７℃で３日間インキュベーションした後、一定量を取り出しＳＤＳ－ＰＡＧＥを用い、電気泳動を行なった。電気泳動後、0.2%クーマシー・ブリリアント・ブルー（Coomassie Brilliant Blue）Ｒ－２５０で染色後、デンシトメーターにより二量体の生成量を定量した。本発明化合物はインキュベーション前に添加し、さまざまな濃度における二量体生成に対する抑制効果を調べて、IC_{50}値を求めた。

(2) 結果を表２５に示す。

【００９６】

【表２５】

実施例番号	IC_{50}（μM）
1	4.4
1（1）	2.9
1（5）	9.2
1（３０）	4.4
1（３７）	1.5
1（４０）	2.7
1（４４）	5.5

【００９７】本発明化合物の抗酸化作用は以下に述べる過酸化脂質生成抑制効果を調べるスクリーニング系により確認された。

(1) 実験方法

一晩絶食させた雄性 Sprague Dawley ラットをエーテル麻酔下、氷冷した0.9%塩化ナトリウム水溶液で門脈より潅流し、肝組織を摘出した。摘出肝を氷冷した1.15%塩化カリウム水溶液を用い、１０%ホモジネートとした。得られたホモジネート２００μｌに$FeCl_2$ ２００ｍＭを加え、３７℃で１時間インキュベートした。オオカワ（Ohkawa）らの方法［Analytical Biochemistry, 95, 351 (1979)参照］に従い、過酸化脂質の生成量をチオバルビツール酸（ＴＢＡ）法により測定した。本発明化合物は、インキュベーション前に添加し、その効果を調べ、IC_{50}値を算出した。

(2) 結果を表２６に示す。

【００９８】

【表２６】

実施例番号	IC_{50}（μM）
1	3.8
1（5）	3.7
1（２９）	2.9
1（３２）	1.8
1（３９）	0.82
1（２５）	１６
1（４７）	0.56
1（４１）	0.45
3	0.96

【００９９】表２５および表２６から、本発明化合物、その非毒性塩およびその酸付加塩はメイラード反応阻害作用および抗酸化作用を有することがわかる。

【０１００】

【毒性】本発明化合物の毒性は十分に低いものであり、医薬品として十分安全に使用できることが確認された。

【０１０１】

【医薬品への適用】一般式（Ｉ）で示される本発明化合物、およびそれらの酸付加塩は、メイラード反応を阻害するので、種々の糖尿病合併症、例えば冠動脈性心疾患、末梢循環障害、脳血管障害、糖尿病性神経症、腎症、動脈硬化、関節硬化症、白内障および網膜症、また老化によりひき起こされる疾患、例えばアテローム性動脈硬化症、老人性白内障および癌の治療および／または予防に有用である。また、一般式（Ｉ）で示される本発明化合物、およびそれらの酸付加塩は、抗酸化作用、すなわち、フリーラジカルの反応を抑制する作用をも併せ持つため、過酸化脂質産生が原因となる種々の疾患、例えば動脈硬化、糖尿病、心筋梗塞、末梢循環障害、脳血管障害、癌、炎症、消化器疾患および老化の治療および／または予防に有用である。

【０１０２】一般式（Ｉ）で示される本発明化合物、お

よびそれらの酸付加塩を上記の目的で用いるには、通常全身的あるいは局所的に、経口または非経口で投与される。投与量は年令、体重、症状、治療効果、投与方法、処理時間等により異なるが、通常成人ひとり当り、一回につき１ｍｇ～１０００ｍｇの範囲で１日１回から数回経口投与されるか、あるいは成人ひとり当り、１回につき0.１ｍｇ～１００ｍｇの範囲で１日１回から数回非経口投与（好ましくは静脈内投与）される。もちろん前記したように、投与量は種々の条件で変動するので、上記投与量範囲より少ない量で十分な場合もあるし、また範囲を越えて必要な場合もある。

【０１０３】本発明化合物を投与する際には、経口投与のための固体組成物、液体組成物およびその他の組成物、非経口投与のための注射剤、外用剤、坐剤等が用いられる。

【０１０４】経口投与のための固体組成物には、錠剤、丸剤、カプセル剤、散剤、顆粒剤などが含まれる。カプセル剤には、ハードカプセルおよびソフトカプセルが含まれる。このような固体組成物においては、ひとつまたはそれ以上の活性物質が、少なくともひとつの不活性な希釈剤、例えばヒドロキシプロピルセルロース、微結晶セルロース、デンプン、ポリビニルピロリドン、メタケイ酸アルミン酸マグネシウムと混合される。組成物は、常法に従って、不活性な希釈剤以外の添加剤、例えばステアリン酸マグネシウムのような潤滑剤、繊維素グリコール酸カルシウムのような崩壊剤、グルタミン酸またはアスパラギン酸のような溶解補助剤を含有していてもよい。錠剤または丸剤は必要により白糖、ゼラチン、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロースフタレートなどの胃溶性あるいは腸溶性物質のフィルムで被膜してもよいし、また２以上の層で被膜してもよい。さらにゼラチンのような吸収されうる物質のカプセルも包含される。経口投与のための液体組成物は、薬剤的に許容される乳濁剤、溶液剤、懸濁剤、シロップ剤、エリキシル剤等を含み、一般的に用いられる不活性な希釈剤（例えば精製水、エタノール）を含んでいてもよい。この組成物は不活性な希釈剤以外に湿潤剤、懸濁剤のような補助剤、甘味剤、風味剤、芳香剤、防腐剤を含有していてもよい。経口投与のためのその他の組成物としては、ひとつまたはそれ以上の活性物質を含み、それ自体公知の方法により処方されるスプレー剤が含まれる。この組成物は不活性な希釈剤以外に亜硫酸水素ナトリウムのような安定剤と等張性を与えるような緩衝剤、例えば塩化ナトリウム、クエン酸ナトリウムあるいはクエン酸を含有してもよい。スプレー剤の製造方法は、例えば米国特許第2868691 号および同第3095355 号明細書に詳しく記載されている。

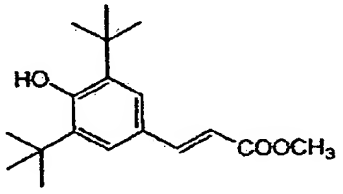
【０１０５】本発明による非経口投与のための注射剤としては、無菌の水性または非水性の溶液剤、懸濁剤、乳濁剤を包含する。水性の溶液剤、懸濁剤としては、例えば注射用蒸留水および生理食塩水が含まれる。非水溶性の溶液剤、懸濁剤としては、例えばプロピレングリコール、ポリエチレングリコール、オリーブ油のような植物油、エタノールのようなアルコール類、ポリソルベート８０等がある。このような組成物は、さらに防腐剤、湿潤剤、乳化剤、分散剤、安定化剤、溶解補助剤（例えば、グルタミン酸、アスパラギン酸）のような補助剤を含んでもよい。これらは例えばバクテリア保留フィルターを通すろ過、殺菌剤の配合または照射によって無菌化される。これらはまた無菌の固体組成物を製造し、使用前に無菌水または無菌の注射用溶媒に溶解して使用することもできる。非経口投与のためのその他の組成物としては、ひとつまたはそれ以上の活性物質を含み、常法により処方される外用液剤、軟膏のような塗布剤、直腸内投与のための坐剤および膣内投与のためのペッサリー等が含まれる。

【０１０６】

【参考例および実施例】以下、参考例および実施例によって本発明を詳述するが、本発明はこれらに限定されるものではない。クロマトグラフィーによる分離の箇所に記載されているカッコ内の溶媒は、使用した展開溶媒を示し、割合は体積比を表わす。また、ＮＭＲの箇所に記載されているカッコ内は測定溶媒を示している。

【０１０７】参考例１

【化６５】

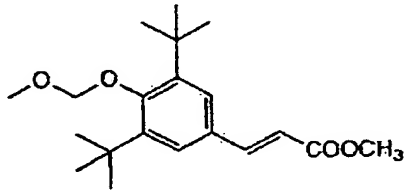


【０１０８】３，５－ジ－ｔ－ブチル－４－ヒドロキシベンズアルデヒド（11.7ｇ）とトリフェニルホスホリデン酢酸メチルエステル（18.4ｇ）のベンゼン溶液（５０ｍｌ）をアルゴン下、１時間還流し、濃縮した。残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：１０→５：１）で精製して、下記の物性値を有する標題化合物（14.1ｇ）を得た。

ＴＬＣ：Ｒｆ 0.51（酢酸エチル：ｎ－ヘキサン＝１：５）。

【０１０９】参考例２

【化６６】



【０１１０】水素化ナトリウム（６０％含有：1.65ｇ）のジメチルホルムアミド（DMF）懸濁液に、－７８

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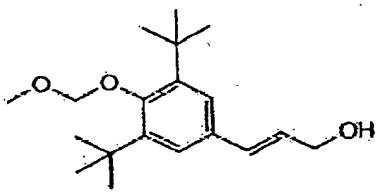
℃、アルゴン下で参考例１で製造した化合物（8.0ｇ）のＤＭＦ溶液（２０ｍｌ）を加えた。混合物を０℃で１５分間撹拌した。反応混合物に０℃でメトキシメチルクロライド（2.5ｍｌ）を加え、１０分間撹拌し、さらに室温で２時間撹拌した。さらに、水素化ナトリウム（６０％含有；0.83ｇ）およびメトキシメチルクロライド（1.2ｍｌ）を加え、室温で１時間撹拌した。反応溶液に水を加え、酢酸エチルで抽出した。有機層を水で洗浄し、硫酸マグネシウムで乾燥後、濃縮した。残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：２０）で精製して、下記の物性値を有する標題化合物（8.80ｇ）を得た。

【０１１１】ＴＬＣ：Ｒｆ 0.40（酢酸エチル：ｎ－ヘキサン＝１：９）、

ＮＭＲ（$CDCl_3$）：δ 7.65(1H,d)，7.44(2H,s)，6.34(1H,d)，4.91(2H,s)，3.80(3H,s)，3.65(3H,s)，1.45(18H,s)。

【０１１２】参考例３

【化６７】



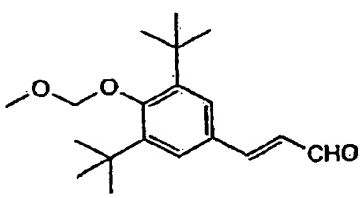
【０１１３】参考例２で製造した化合物（8.79ｇ）の塩化メチレン溶液（３０ｍｌ）に、－７８℃、アルゴン下で、１Ｍジイソブチルアルミニウムハイドライドのトルエン溶液（65.7ｍｌ）を加えた。混合溶液を－７８℃で３０分間撹拌した。反応溶液に水を加え、１Ｎ塩酸で中和し、クエン酸で酸性にした後、酢酸エチルで抽出した。有機層を飽和食塩水、飽和炭酸水素ナトリウム、飽和食塩水で順次洗浄し、硫酸マグネシウムで乾燥後、濃縮した。残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：６）で精製して、下記の物性値を有する標題化合物（8.03ｇ）を得た。

【０１１４】ＴＬＣ：Ｒｆ 0.11（酢酸エチル：ｎ－ヘキサン＝１：９）、

ＮＭＲ（$CDCl_3$）：δ 7.30(2H,s)，6.57(1H,d)，6.27(1H,dt)，4.89(2H,s)，4.30(2H,s)，3.64(3H,s)，1.45(18H,s)。

【０１１５】参考例４

【化６８】



【０１１６】参考例３で製造した化合物（8.0ｇ）の塩

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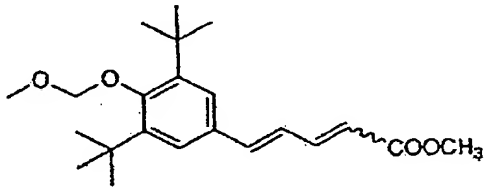
化メチレン溶液（２５ｍｌ）に、トリエチルアミン（３０ｍｌ）、ジメチルスルホキシド（ＤＭＳＯ）（２５ｍｌ）およびスルファートリオキシドピリジン錯体（16.6ｇ）を０℃、アルゴン下で加えた。混合物を０℃で５分間撹拌した後、さらに室温で３０分間撹拌した。反応溶液を酢酸エチルと水の混合溶液に注いた。有機層を飽和食塩水、クエン酸、飽和食塩水、飽和炭酸水素ナトリウムおよび飽和食塩水で順次洗浄し、硫酸マグネシウムで乾燥後、濃縮して、下記の物性値を有する標題化合物を得た。

【０１１７】ＴＬＣ：Ｒｆ ０80（酢酸エチル：ｎ－ヘキサン＝１：４）、

ＮＭＲ（$CDCl_3$）：δ 9.68(1H,d)，7.49(2H,s)，7.45(1H,d)，6.65(1H,d)，4.93(2H,s)，3.66(3H,s)，1.46(18H,s)。

【０１１８】参考例５

【化６９】

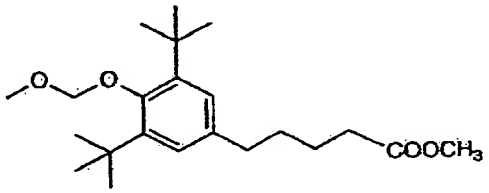


【０１１９】参考例４で製造した化合物とトリフェニルホスホリデン酢酸メチルエステル（17.52ｇ）のベンゼン溶液（５０ｍｌ）をアルゴン下、１３時間還流し、濃縮した。残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：２０）で精製して、下記の物性値を有する標題化合物（8.05ｇ）を得た。

ＴＬＣ：Ｒｆ 0.40（酢酸エチル：ｎ－ヘキサン＝１：１０）。

【０１２０】参考例６

【化７０】



【０１２１】参考例５で製造した化合物（8.04ｇ）およびパラジウム炭素（８００ｍｇ）のメタノール溶液（２０ｍｌ）を水素ガス下、室温で１６時間撹拌した。反応溶液をセライトろ過し、濃縮した。残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：２０）で精製して、下記の物性値を有する標題化合物（7.30ｇ）を得た。

ＴＬＣ：Ｒｆ 0.37（酢酸エチル：ｎ－ヘキサン＝１：１０）。

【０１２２】参考例７

【化７１】

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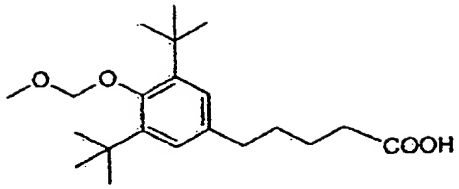
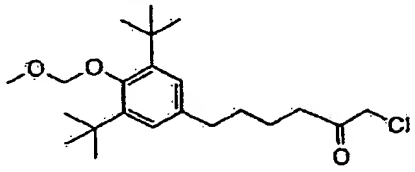


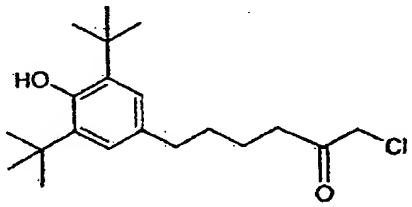
【０１２３】参考例６で製造した化合物（3.65ｇ）のメタノール溶液（１０ｍｌ）に、２Ｎ水酸化ナトリウム（３５ｍｌ）を０℃で加えた。混合溶液を室温で６時間＊



【０１２５】参考例７で製造した化合物のベンゼン溶液（１０ｍｌ）に、オキサリルクロライド（1.05ｍｌ）およびDMF（３滴）を０℃、アルゴン下で加えた。混合溶液を室温で１時間撹拌した。反応溶液を濃縮し、残留物をジエチルエーテルに溶解した。溶液に０℃で、ジアゾメタンのエタノール溶液をガスが発生しなくなるまで滴下し、さらに４Ｎ塩酸の１，４－ジオキサン（１０ｍｌ）溶液を０℃でガスが発生しなくなるまで滴下した。溶液を酢酸エチルで希釈し、飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後、濃縮した。残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：２０）で精製して、標題の混合化合物（3.54ｇ）を得た。

【０１２６】参考例９

【化７３】



【０１２７】参考例８で製造した化合物は、水酸基が保護されている物とされていない物との混合物のため、その混合物の１，４－ジオキサン（１０ｍｌ）と水（0.5ｍｌ）の混合溶液に、４Ｎ塩酸の１，４－ジオキサン溶液（１０ｍｌ）を０℃で加えた。混合溶液を室温で１２時間撹拌した。反応溶液を濃縮し、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後、濃縮した。残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：２０）で精製して、下記の物性値を有する標題化合物（3.18ｇ）を得た。

【０１２８】ＴＬＣ：Ｒｆ　0.42（酢酸エチル：ｎ－ヘキサン＝１：１０）、

NMR（$CDCl_3$）：δ 6.96(2H,s)，5.03(1H,s)，4.05(2H,s)，2.62(2H,t)，2.54(1H,t)，1.50-1.80(4H,m)，1.43(18H,s)。

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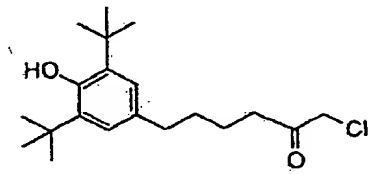
＊撹拌し、濃縮した。残留物を１Ｎ塩酸で酸性化し、酢酸エチルで抽出した。有機層を飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後、濃縮して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ　0.07（酢酸エチル：ｎ－ヘキサン＝１：１０）。

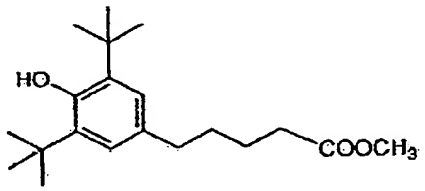
【０１２４】参考例８

【化７２】



【０１２９】参考例１０

【化７４】



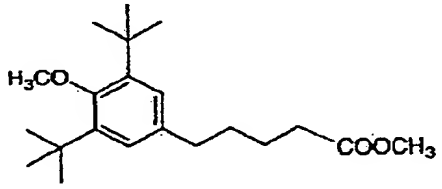
【０１３０】参考例６で製造した化合物（3.65ｇ）を用い、参考例９と同様に操作して、下記の物性値を有する標題化合物（3.58ｇ）を得た。

ＴＬＣ：Ｒｆ　0.41（酢酸エチル：ｎ－ヘキサン＝１：１０）、

NMR（$CDCl_3$）：δ 6.96(2H,s)，5.03(1H,s)，3.67(3H,s)，2.53(2H,t)，2.35(1H,t)，1.50-1.80(4H,m)，1.43(18H,s)。

【０１３１】参考例１１

【化７５】



【０１３２】参考例１０で製造した化合物（3.20ｇ）のDMF溶液（２５ｍｌ）に、水素化ナトリウム（６０％含有：1.20ｇ）を加えた。懸濁液を０℃で３０分間撹拌した。反応混合物にヨウ化メタン（2.49ｍｌ）を０℃で加えた。混合物を室温で２４時間撹拌した。反応混合物に飽和塩化アンモニウムを加え、酢酸エチルで抽出した。有機層を飽和塩化アンモニウムおよび飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後、濃縮した。残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：２０）で精製して、下記の物性値を有する標題化合物（3.30ｇ）を得た。

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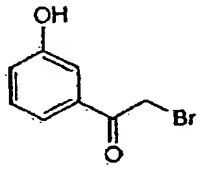
ＴＬＣ：Ｒｆ 0.38（酢酸エチル：ｎ－ヘキサン＝１：１０）。

【０１３３】参考例１２

【化７６】

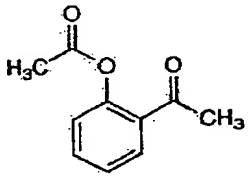


【０１３４】３′－ヒドロキシアセトフェノン（1.0ｇ）の酢酸およびテトラハイドロフラン（ＴＨＦ）の混合溶液（3.0ｍｌ＋0.5ｍｌ）に、臭素（３７８μｌ）をゆっくり加えた。混合物を室温で15時間撹拌した。反応溶液を酢酸エチルで希釈し、飽和炭酸水素ナトリウム、水および飽和食塩水で順次洗浄し、硫酸マグネシウムで乾燥後、濃縮した。残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：５）で精製して、下記の物性値を有する標題化合物（1.10ｇ）を得た。

ＴＬＣ：Ｒｆ 0.32（酢酸エチル：ｎ－ヘキサン＝１：３）。

【０１３５】参考例１３

【化７７】

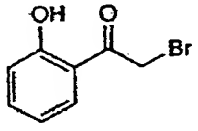


【０１３６】２′－ヒドロキシアセトフェノン（1.5ｇ）の塩化メチレン溶液（１０ｍｌ）に、ピリジン（1.5ｍｌ）、無水酢酸（1.5ｍｌ）および４－ジメチルアミノピリジン（0.03ｇ）を加えた。混合溶液を室温で３時間撹拌し、濃縮した。残留物を酢酸エチルで希釈し、水、１Ｎ塩酸および飽和食塩水で順次洗浄し、硫酸マグネシウムで乾燥後、濃縮して、下記の物性値を有する標題化合物（2.8ｇ）を得た。

ＴＬＣ：Ｒｆ 0.15（酢酸エチル：ｎ－ヘキサン＝１：１０）。

【０１３７】参考例１４

【化７８】



【０１３８】参考例１３で製造した化合物（８００ｍｇ）のＴＨＦ溶液（１０ｍｌ）に、ピリジニウム・ブロマイド・パーブロマイド（1.58ｇ）を加えた。混合物を室温で１時間撹拌した。反応溶液を酢酸エチルで希釈し、水で洗浄し、硫酸マグネシウムで乾燥後、濃縮した。残留物を一晩放置した後、カラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：２０）で精製して、下記の物性値を有する標題化合物（５９３ｍｇ）を得た。

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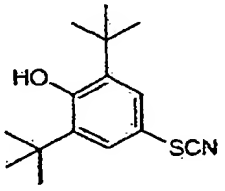
ＴＬＣ：Ｒｆ 0.30（酢酸エチル：ｎ－ヘキサン＝１：３）。

【０１３９】参考例１５

【化７９】

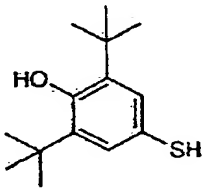


【０１４０】２，６－ジ－ｔ－ブチルフェノール（５０ｇ）およびチオシアン酸アンモニウム（3.9ｇ）のメタノール溶液（２５ｍｌ）に、塩素ガスを２０分間０℃で注入した後、アルゴン置換し、アンモニアガスを２０分間０℃で注入し、さらに３０分間撹拌した。反応溶液を氷水中に注ぎ、一晩放置後、沈殿物をろ取した。沈殿物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：１５）で精製して、下記の物性値を有する標題化合物（5.2ｇ）を得た。

ＴＬＣ：Ｒｆ 0.38（酢酸エチル：ｎ－ヘキサン＝１：１５）。

【０１４１】参考例１６

【化８０】

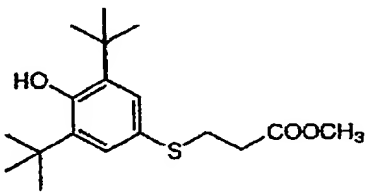


【０１４２】参考例１５で製造した化合物（4.8ｇ）のアセトン溶液（２０ｍｌ）に、トリフェニルホスフィン（4.8ｇ）および水（0.66ｍｌ）を０℃で加えた後、室温で３時間撹拌した。反応溶液を濃縮し、残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：３０）で精製して、下記の物性値を有する標題化合物（3.0ｇ）を得た。

ＴＬＣ：Ｒｆ 0.58（酢酸エチル：ｎ－ヘキサン＝１：５）。

【０１４３】参考例１７

【化８１】



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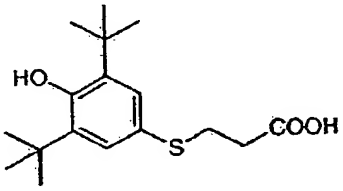
【０１４４】参考例１６で製造した化合物（８１７ｍｇ）のメタノール溶液（５ｍｌ）に、トリエチルアミン（８２μｌ）およびアクリル酸メチル（９２７μｌ）を加え、室温で２０分間撹拌した。反応溶液を濃縮し、残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：２０）で精製して、下記の物性値を有する標題化合物（８１７ｍｇ）を得た。

ＴＬＣ：Ｒｆ　0.15（酢酸エチル：ｎ－ヘキサン＝１：２０）。

【０１４５】参考例１８

【化８２】

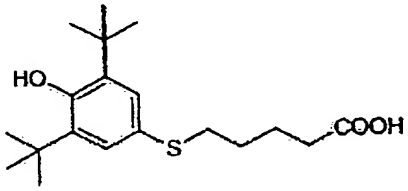


【０１４６】参考例１７で製造した化合物（８１５ｍｇ）のメタノール溶液（５ｍｌ）に、水酸化リチウム（５２８ｍｇ）水溶液を加え、室温で１時間撹拌した。反応溶液を濃縮した。残留物に１Ｎ塩酸水溶液をｐＨが１になるまで加え、酢酸エチルで抽出した。有機層を水および飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後、濃縮して、下記の物性値を有する標題化合物（７７６ｍｇ）を得た。

ＴＬＣ：Ｒｆ　0.34（酢酸エチル：ｎ－ヘキサン＝１：１）

【０１４７】参考例１９

【化８３】



【０１４８】参考例１６で製造した化合物（７６０ｍｇ）のＤＭＦ溶液（１５ｍｌ）に、ジイソプロピルエチルアミン（６６７μｌ）および５－ブロム吉草酸（６９４ｍｇ）を加え、室温で一晩撹拌した。反応溶液に、氷水を加え、酢酸エチルで抽出した。有機層を水および飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後、濃縮した。残留物をカラムクロマトグラフィ（クロロホルム：メタノール＝２０：１）で精製して、標題化合物（４８５ｍｇ）を得た。

【０１４９】参考例２０

【化８４】

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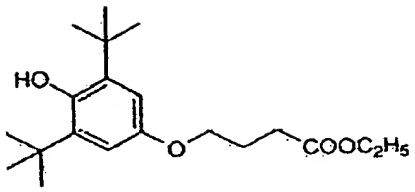
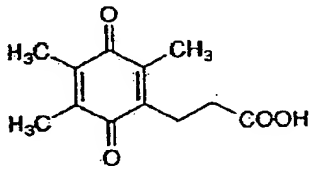


【０１５０】２，５－ジ－ｔ－ブチルハイドロキノン（１８ｇ）のＤＭＦ溶液（１５ｍｌ）に、水素化ナトリウム（３５６ｍｇ）を０℃で加え、室温で３０間撹拌した。反応溶液に４－ブロムブチル酸エチル（1.3ｍｌ）を０℃で加え、６０℃で一晩撹拌した。反応溶液に、氷水を加え酢酸エチルで抽出した。有機層を水および飽和食塩水で洗浄し、硫酸マグネシウムで乾燥した。溶媒を留去し、残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１・３０）で精製して、下記の物性値を有する標題化合物（1.73ｇ）を得た。

ＴＬＣ：Ｒｆ　0.66（酢酸エチル：ｎ－ヘキサン＝１：３）。

【０１５１】参考例２１

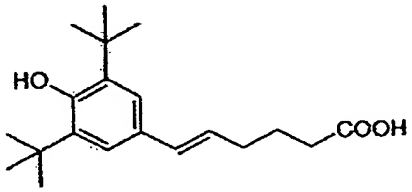
【化８５】



【０１５２】３，６－ジメトキシ－２，４，５－トリメチルベンズアルデヒドを用いて、参考例１→参考例６→参考例７と同様にして得られた、３－（３，６－ジメトキシ－２，４，５－トリメチルフェニル）プロパン酸（2.07ｇ）の５０％アセトニトリル水溶液（５０ｍｌ）に、０℃でセリウムアンモニウムニトレート（9.92ｇ）の５０％アセトニトリル水溶液（２５ｍｌ）を加え、１５分間撹拌した。反応溶液に、炭酸水素ナトリウム水溶液を注ぎ、酢酸エチルで抽出した。有機層を水および飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後濃縮して標題化合物（0.91ｇ）を得た。

【０１５３】参考例２２

【化８６】



【０１５４】水素化ナトリウム（６０％含有：８６５ｍｇ）のＤＭＳＯ溶液（２０ｍｌ）懸濁液を、７０℃で１時間撹拌した。５－（トリフェニルホスフィン）ペンタン酸ブロマイド（4.78ｇ）のＤＭＳＯ溶液（１０ｍｌ）を、１０～２０℃で滴下し、室温で３０分間撹拌した。

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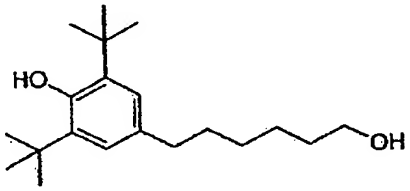
３，５－ジ－ｔ－ブチル－４－ヒドロキシベンズアルデヒド（1.00ｇ）のＤＭＳＯ溶液（１０ｍｌ）を１０～２０℃で滴下し、室温で一晩撹拌した。反応溶液を水に注ぎ、２Ｎ塩酸を加え、ジエチルエーテルで抽出した。有機層を水および飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後、濃縮した。残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：３）で精製して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.15（酢酸エチル：ｎ－ヘキサン＝１：３）。

【０１５５】参考例２３

【化８７】

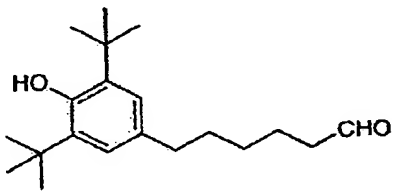


【０１５６】参考例２２で製造した化合物を用いて、参考例６と同様に操作して得られた化合物、６－（３，５－ｔ－ブチル－４－ヒドロキシフェニル）－５－ヘキセン酸（１００ｍｇ）のＴＨＦ溶液（３ｍｌ）に、０℃でリチウムアルミニウムハイドライド（３０ｍｇ）を加え、室温で１時間撹拌した。反応溶液に、飽和硫酸ナトリウム水溶液を滴下し撹拌後、硫酸ナトリウム加え、ろ過した。ろ液を濃縮し、残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：５→１：３）で精製して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.20（酢酸エチル：ｎ－ヘキサン＝１：３）。

【０１５７】参考例２４

【化８８】



【０１５８】オキサリルクロライド（0.025ｍｌ）の塩化メチレン溶液（１ｍｌ）を－７０℃に冷却した。そこにＤＭＳＯ（0.04ｍｌ）の塩化メチレン溶液（１ｍｌ）を滴下した。混合溶液を１０分間撹拌した。反応溶液に、参考例２３で製造した化合物の塩化メチレン溶液（１ｍｌ）を加え３０分間撹拌した。反応溶液に、トリエチルアミン（0.2ｍｌ）を加え、ドライアイス浴を外して３０分間撹拌した。反応溶液をエーテルで抽出した。有機層を水および飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後、濃縮して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.59（酢酸エチル：ｎ－ヘキサン＝１：３）。

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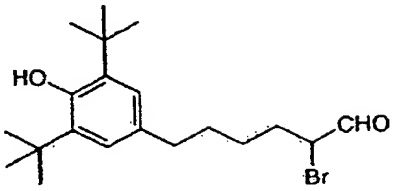
【０１５９】参考例２５

【化８９】

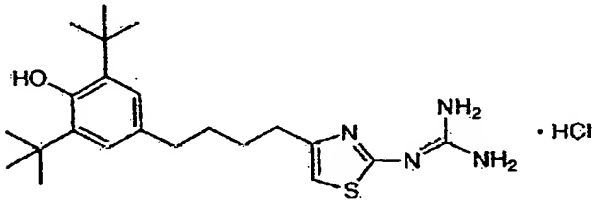


【０１６０】参考例２４で製造した化合物のクロロホルム溶液（１０ｍｌ）に、臭素（0.07ｍｌ）のクロロホルム溶液（0.25ｍｌ）を、－２０℃で滴下した。混合溶液を－２０℃で１時間撹拌後、室温に戻した。再び－２０℃に冷却し、臭素（0.04ｍｌ）のクロロホルム溶液（0.12ｍｌ）を滴下し、－２０℃で３０分間撹拌した。反応溶液を濃縮し、残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：３０）で精製して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.43（酢酸エチル：ｎ－ヘキサン＝１：１０）。

【０１６１】実施例１

【化９０】



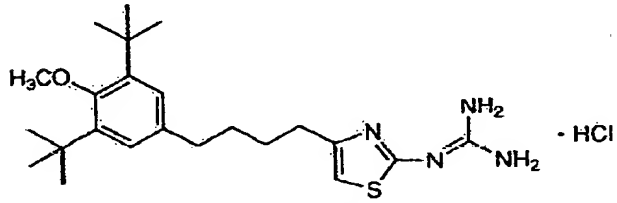
【０１６２】参考例９で製造した化合物（2.0ｇ）およびグアニジノチオウレア（６６２ｍｇ）のメタノール溶液（２０ｍｌ）を１２時間還流した。反応溶液を濃縮し、ジエチルエーテルで再結晶して、下記の物性値を有する標題化合物（2.42ｇ）を得た。

【０１６３】ＴＬＣ：Ｒｆ 0.34（酢酸エチル：酢酸：水＝２０：１：１）、

ＮＭＲ（$CDCl_3$）：δ 6.96(2H, s), 6.46(1H, s), 5.04(1H, s), 2.67(2H, t), 2.54(2H, t), 1.70-1.62(4H, m), 1.43(18H, s)。

【０１６４】実施例１（１）

【化９１】



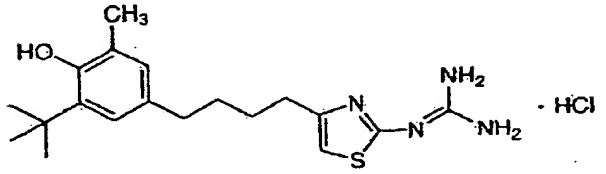
【０１６５】参考例１１で製造した化合物を用いて、参考例７→参考例８→実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.33（酢酸エチル：酢酸：水＝２０：

１：１）、
NMR（$CDCl_3$）：δ 7.02(2H,s)，6.46(1H,s)，3.67(3H,s)，2.66(2H,t)，2.55(2H,t)，1.73-1.65(4H,m)，1.41(18H,s)。

【０１６６】実施例１（２）

【化９２】



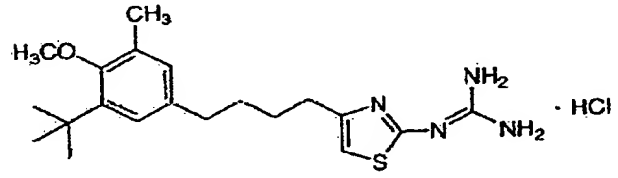
【０１６７】相当するアルデヒドを用いて、参考例１→参考例２→参考例３→参考例４→参考例５→参考例６→参考例７→参考例８→参考例９→実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.34（酢酸エチル：酢酸：水＝２０：１：１）、

NMR（$CDCl_3$）：δ 6.91(1H,d)，6.79(1H,d)，6.45(1H,s)，4.89(1H,s)，2.64(2H,t)，2.52(2H,t)，2.24(3H,s)，1.68-1.58(4H,m)，1.39(9H,s)。

【０１６８】実施例１（３）

【化９３】



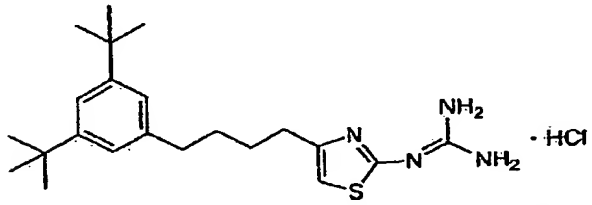
【０１６９】相当するアルデヒドを用いて、参考例１→参考例２→参考例３→参考例４→参考例５→参考例６→参考例１０→参考例１１→参考例７→参考例８→実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.35（酢酸エチル：酢酸：水＝２０：１：１）、

NMR（$CDCl_3$）：δ 6.94(1H,d)，6.85(1H,d)，6.46(1H,s)，3.75(3H,s)，2.66(2H,t)，2.54(2H,t)，2.29(3H,s)，1.70-1.60(4H,m)，1.37(9H,s)。

【０１７０】実施例１（４）

【化９４】



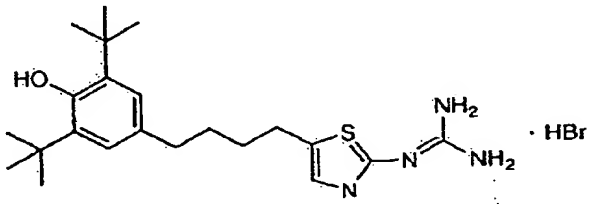
【０１７１】相当するアルデヒドを用いて、参考例１→参考例３→参考例４→参考例５→参考例６→参考例７→参考例８→実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.44（酢酸エチル：酢酸：水＝２０：１：１）、

NMR（$CDCl_3$）：δ 7.25(1H,s)，7.02(2H,d)，6.44(1H,s)，2.70-2.58(4H,m)，1.75-1.60(4H,m)，1.30(18H,s)。

【０１７２】実施例１（５）

【化９５】



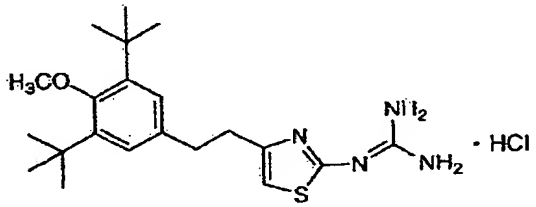
【０１７３】参考例２５で製造した化合物を用いて、実施例１と同様に操作して下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.49（クロロホルム・メタノール：酢酸＝２０：２：１）、

NMR（CD_3OD）：δ 7.12(1H,s)，6.93(2H,s)，2.80(2H,t)，2.54(2H,t)，1.73-1.52(4H,m)，1.41(18H,s)。

【０１７４】実施例１（６）

【化９６】



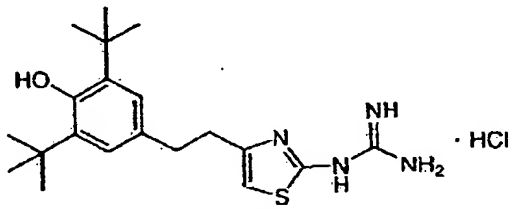
【０１７５】参考例１で製造した化合物を用いて、参考例１１→参考例６→参考例７→参考例８→実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.73（酢酸エチル：酢酸：水＝２０：１：１）、

NMR（$CDCl_3$）：δ 7.04(2H,s)，6.22(1H,s)，3.67(3H,s)，2.88(4H,s)，1.41(18H,s)。

【０１７６】実施例１（７）

【化９７】



【０１７７】参考例２で製造した化合物を用いて、参考例６→参考例７→参考例８→参考例９→実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.78（酢酸エチル：酢酸：水＝１２：２：１）、

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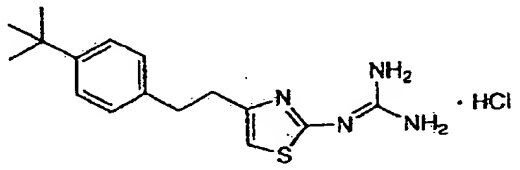
NMR (DMSO-d_6) : δ 8.28-8.25(4H, m), 6.87(2H, s), 6.69(1H, s), 2.84(4H, s), 1.35(18H, s)。

【０１７８】実施例１（８）～１（１１）

相当するアルデヒドを用いて、参考例１→参考例６→参考例７→参考例８→実施例１と同様に操作して、下記の化合物を得た。

【０１７９】実施例１（８）

【化９８】

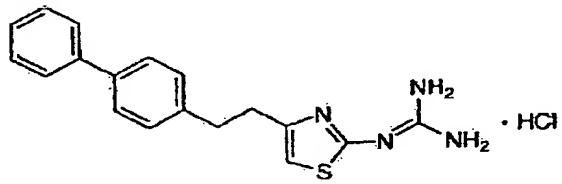


【０１８０】ＴＬＣ：Ｒｆ 0.37（酢酸エチル：酢酸：水＝２０：１：１）、

NMR ($CDCl_3$+CD_3OD(１滴)) : δ 7.33-7.28(2H, m), 7.12-7.10(2H, m), 6.47(1H, s), 2.93(4H, s), 1.30(9H, s)。

【０１８１】実施例１（９）

【化９９】

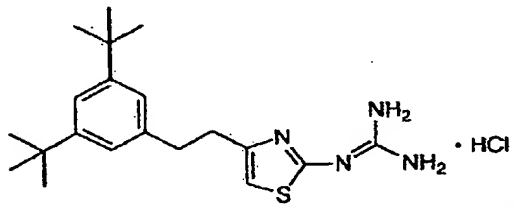


【０１８２】ＴＬＣ：Ｒｆ 0.35（酢酸エチル：酢酸：水＝２０：１：１）、

NMR (CD_3OD) : δ 7.90-7.25(9H, m), 6.74(1H, s), 3.04(4H, s)。

【０１８３】実施例１（１０）

【化１００】



【０１８４】ＴＬＣ：Ｒｆ 0.37（酢酸エチル：酢酸：水＝２０：１：１）、

NMR ($CDCl_3$) : δ 7.26(1H, s), 7.00(2H, d), 6.47(1H, s), 2.94(4H, s), 1.31(18H, s)。

【０１８５】実施例１（１１）

【化１０１】

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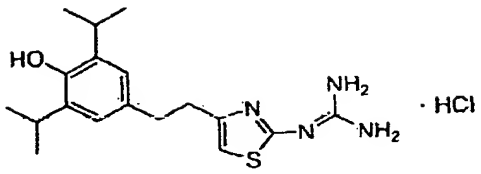


【０１８６】ＴＬＣ：Ｒｆ 0.39（酢酸エチル：酢酸：水＝２０：１：１）、

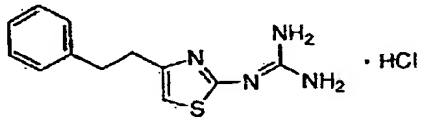
NMR ($CDCl_3$) : δ 6.79(2H, s), 6.47(1H, s), 5.16(1H, s), 3.28-3.14(2H, m), 2.93-2.86(4H, m), 1.22(12H, d)。

【０１８７】実施例１（１２）～（２０）

相当するカルボン酸を用いて、参考例８→実施例１と同様に操作して、下記の化合物を得た。

【０１８８】実施例１（１２）

【化１０２】

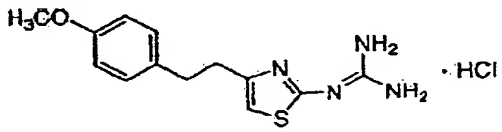


【０１８９】ＴＬＣ：Ｒｆ 0.44（酢酸エチル：酢酸：水＝２０：２：１）、

NMR ($CDCl_3$: CD_3OD＝２０：１) : δ 7.31-7.14(5H, m), 6.33(1H, s), 3.45(4H, s)。

【０１９０】実施例１（１３）

【化１０３】

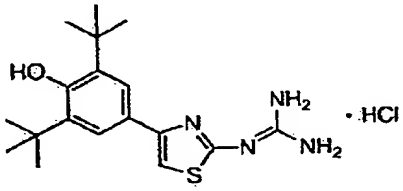


【０１９１】ＴＬＣ：Ｒｆ 0.43（酢酸エチル：酢酸：水＝２０：２：１）、

NMR ($CDCl_3$: CD_3OD＝２０：１) : δ 7.09-6.80(4H, m), 6.41(1H, s), 3.79(4H, s), 2.90(2H, s)。

【０１９２】実施例１（１４）

【化１０４】



【０１９３】ＴＬＣ：Ｒｆ 0.55（酢酸エチル：酢酸：水＝２０：１：１）、

NMR ($CDCl_3$) : δ 7.58(2H, s), 6.68(1H, s), 1.46(18H, s)。

【０１９４】実施例１（１５）

【化１０５】

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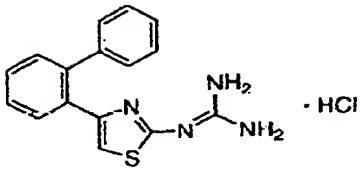
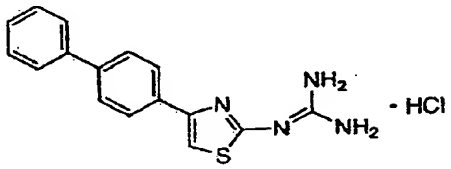


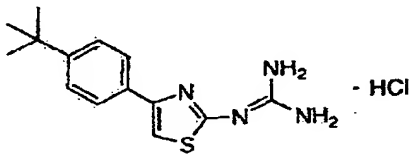
【０１９５】ＴＬＣ：Ｒｆ ０.６４（クロロホルム：メタノール：酢酸＝１６：３：１）、
NMR (DMSO-d_6) ：δ 12.35(1H, brs), 7.89(4H, brs), 7.75(1H, m), 7.48(2H, t), 7.34(4H, m), 7.17(2H, m), 7.08(1H, s)。

【０１９６】実施例１（１６）
【化１０６】



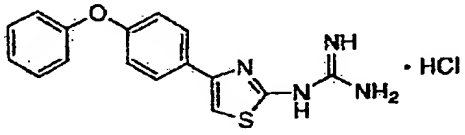
【０１９７】ＴＬＣ：Ｒｆ ０.６５（クロロホルム：メタノール：酢酸＝８：１：１）、
NMR (DMSO-d_6) ：δ 12.63(1H, brs), 8.36(4H, brs), 8.05(2H, d), 7.83(1H, s), 7.74(4H, m), 7.45(3H, m)。

【０１９８】実施例１（１７）
【化１０７】



【０１９９】ＴＬＣ：Ｒｆ ０.７６（クロロホルム：メタノール：酢酸＝１６：３：１）、
NMR (DMSO-d_6) ：δ 12.58(1H, brs), 8.34(4H, brs), 7.85(2H, d), 7.68(1H, s), 7.45(2H, d, J=8Hz), 1.31(9H, s)。

【０２００】実施例１（１８）
【化１０８】



【０２０１】ＴＬＣ：Ｒｆ ０.４９（クロロホルム：メタノール：酢酸＝１８：１：１）、
NMR (DMSO-d_6) ：δ 12.60(1H, brs), 8.27(4H, brs), 7.97(2H, dd,), 7.66(1H, s), 7.42(2H, m), 7.18(2H, m), 7.06(4H, m)。

【０２０２】実施例１（１９）
【化１０９】

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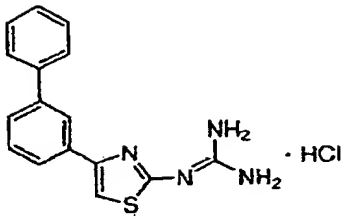
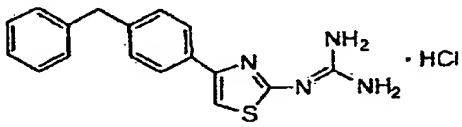


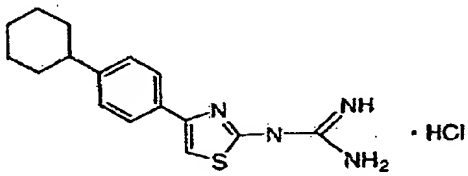
【０２０３】ＴＬＣ：Ｒｆ ０.３８（クロロホルム：メタノール：酢酸＝１８：１：１）、
NMR (DMSO-d_6) ：δ 12.67(1H, brs), 8.37(4H, brs), 8.18(1H, s), 7.99-7.91(2H, m), 7.78-7.36(7H, m)。

【０２０４】実施例１（２０）
【化１１０】



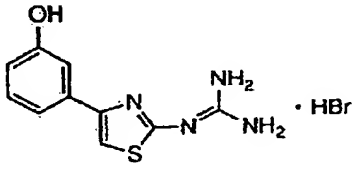
【０２０５】ＴＬＣ：Ｒｆ ０.３９（クロロホルム：メタノール：酢酸＝１８：１：１）、
NMR (DMSO-d_6) ：δ 12.57(1H, brs), 8.32(4H, brs), 7.85(2H, d), 7.68(1H, s), 7.34-7.19(7H, m), 3.98(2H, s)。

【０２０６】実施例１（２１）
【化１１１】



【０２０７】ＴＬＣ：Ｒｆ ０.４０（クロロホルム：メタノール：酢酸＝１８：１：１）、
NMR (DMSO-d_6) ：δ 12.67(1H, brs), 8.37(4H, brs), 7.85(2H, d), 7.67(1H, s), 7.27(2H, d), 2.51(1H, m), 1.78(5H, m), 1.40(5H, m)。

【０２０８】実施例１（２２）
【化１１２】

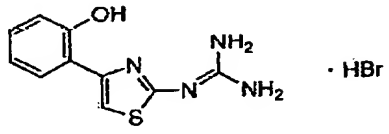


【０２０９】参考例１２で製造した化合物を用いて、実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。
ＴＬＣ：Ｒｆ ０.５１（クロロホルム：メタノール：酢酸＝１５：４：１）、
NMR (DMSO-d_6) ：δ 11.99(1H, brs), 9.52(1H, s),

8.27(4H, s), 7.66(1H, s), 7.27(3H, m), 6.78(1H, m)。

【０２１０】実施例１（２３）

【化１１３】



【０２１１】参考例１４で製造した化合物を用いて、実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.64（クロロホルム：メタノール：酢酸－１５：４：１）、

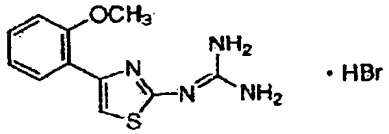
NMR (DMSO-d_6) : δ 11.91(1H, brs), 10.27(1H, s), 8.23(4H, s), 7.96(1H, dd), 7.81(1H, s), 7.17(1H, m), 6.93(2H, m)。

【０２１２】実施例１（２４）～１（２８）

２－ブロモ　３′－メトキシアセトフェノン、４－（クロロアセチル）カテコール、２，３′－ジクロロ－４′，６′－ジメトキシ－２′－ヒドロキシアセトフェノン、２－クロロアセトフェノンまたは２－ブロモ－２′－アセトナフトンを用いて、それぞれ実施例１と同様に操作して、下記の化合物を得た。

【０２１３】実施例１（２４）

【化１１４】

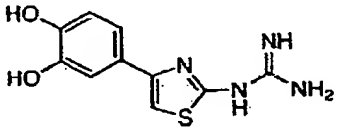


【０２１４】ＴＬＣ：Ｒｆ 0.68（クロロホルム：メタノール：酢酸＝１５：４：１）、

NMR (DMSO-d_6) : δ 11.95(1H, brs), 8.24(4H, s), 8.04(1H, d), 7.77(1H, s), 7.36(1H, m), 7.09(2H, m), 3.93(3H, s)。

【０２１５】実施例１（２５）

【化１１５】

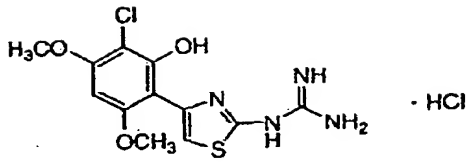


【０２１６】ＴＬＣ：Ｒｆ 0.22（クロロホルム：メタノール：酢酸＝１５：２：１）、

NMR (DMSO-d_6) : δ 12.51(1H, br), 9.25(1H, brs), 9.04(1H, brs), 8.35(4H, brs), 7.39(1H, s), 7.29(1H, d), 7.21(1H, dd), 6.79(1H, d)。

【０２１７】実施例１（２６）

【化１１６】

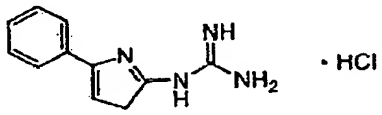


【０２１８】ＴＬＣ：Ｒｆ 0.46（クロロホルム・メタノール＝９：１）、

NMR (DMSO-d_6) : δ 13.75(1H, brs), 7.23(1H, s), 6.49(4H, brs), 6.36(1H, s), 3.92(3H, s), 3.89(3H, s)。

【０２１９】実施例１（２７）

【化１１７】

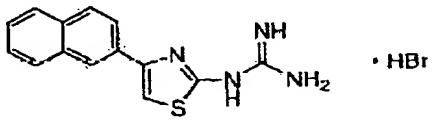


【０２２０】ＴＬＣ：Ｒｆ 0.53（クロロホルム：メタノール：酢酸＝１６：３：１）、

NMR (DMSO-d_6) : δ 12.68(1H, brs), 8.36(4H, s), 7.96(2H, d), 7.76(1H, s), 7.50-7.30(3H, m)。

【０２２１】実施例１（２８）

【化１１８】

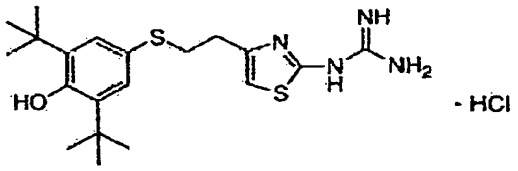


【０２２２】ＴＬＣ：Ｒｆ 0.60（クロロホルム：メタノール：酢酸＝１６：３：１）、

NMR (DMSO-d_6) : δ 12.04(1H, brs), 8.55(1H, s), 8.29(4H, brs), 8.15-7.85(5H, m), 7.63-7.45(2H, m)。

【０２２３】実施例１（２９）

【化１１９】



【０２２４】参考例１８で製造した化合物を用いて、参考例８および実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.62（酢酸エチル：酢酸：水＝２０：１：１）、

NMR ($CDCl_3$) : δ 7.23(2H, s), 6.44(1H, s), 3.10(2H, t), 2.92(2H, t), 1.42(18H, s)。

【０２２５】実施例１（３０）

【化１２０】

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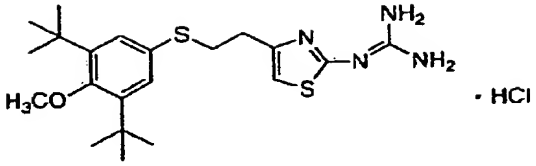
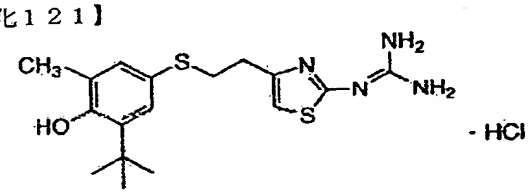
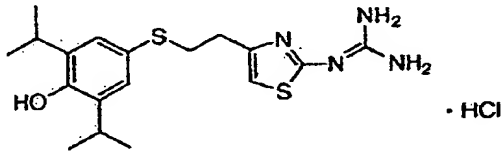


【０２２６】参考例１７で製造した化合物を用いて、参考例１１→参考例１８→参考例８→実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。
ＴＬＣ：Ｒｆ　0.37（酢酸エチル：酢酸：水＝２０：１：１）、
ＮＭＲ（$CDCl_3$）：δ　7.24(2H, s)，6.57(1H, s)，3.68(3H, s)，3.15(2H, t)，2.98(2H, t)，1.41(18H, s)。
【０２２７】実施例１（３１）～１（３２）
相当する化合物を用いて、参考例１５→参考例１６→参考例１７→参考例１８→参考例８→実施例１と同様に操作して、下記の化合物を得た。
【０２２８】実施例１（３１）
【化１２１】



【０２２９】ＴＬＣ：Ｒｆ　0.41（酢酸エチル：酢酸：水＝２０：１：１）、
ＮＭＲ（$CDCl_3$+CD_3OD(１滴)）：δ　7.15(1H, d)，7.00(1H, d)，6.56(1H, s)，3.10(2H, t)，2.90(2H, t)，2.21(3H, s)，1.38(9H, s)。
【０２３０】実施例１（３２）
【化１２２】



【０２３１】ＴＬＣ：Ｒｆ　0.43（酢酸エチル：酢酸：水＝２０：１：１）、
ＮＭＲ（$CDCl_3$）：δ　7.09(2H, s)，6.54(1H, s)，3.19-3.07(4H, m)，2.94-2.85(2H, m)，1.25(12H, d)。
【０２３２】実施例１（３３）～１（３４）
参考例１６で製造した化合物および相当するカルボン酸誘導体を用いて、参考例１８→参考例８→実施例１と同様に操作して、下記の化合物を得た。
【０２３３】実施例１（３３）
【化１２３】

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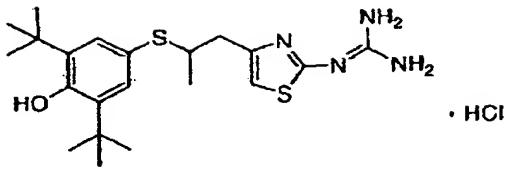
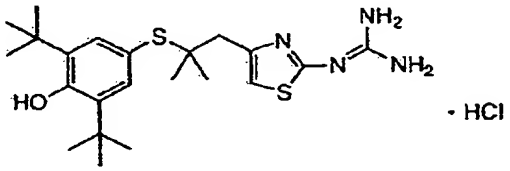
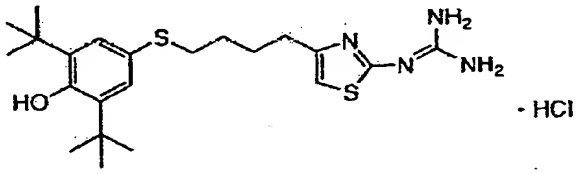


【０２３４】ＴＬＣ：Ｒｆ　0.53（酢酸エチル：酢酸：水＝２０：１：１）、
ＮＭＲ（$CDCl_3$）：δ　7.25(2H, s)，6.57(1H, s)，5.29(1H, s)，3.33(1H, m)，2.95(1H, dd)，2.72(1H, dd)，1.42(18H, s)，1.25(3H, d)。
【０２３５】実施例１（３４）
【化１２４】



【０２３６】ＴＬＣ：Ｒｆ　0.46（酢酸エチル：酢酸：水＝２０：１：１）、
ＮＭＲ（$CDCl_3$）：δ　7.33(2H, s)，6.63(1H, s)，5.37(1H, s)，2.85(2H, s)，1.44(18H, s)，1.21(6H, s)。
【０２３７】実施例１（３５）
【化１２５】



【０２３８】参考例１９で製造した化合物を用いて、参考例８および実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。
ＴＬＣ：Ｒｆ　0.44（酢酸エチル：酢酸：水＝２０：１：１）、
ＮＭＲ（CD_3OD）：δ　7.20(2H, s)，6.71(1H, s)，2.82(2H, t)，2.68(2H, t)，1.81(2H, m)，1.62(2H, m)，1.40(18H, s)。
【０２３９】実施例１（３６）～１（３７）
相当する化合物を用いて、参考例１５→参考例１６→参考例１９→参考例８→実施例１と同様に操作して、下記の化合物を得た。
【０２４０】実施例１（３６）
【化１２６】

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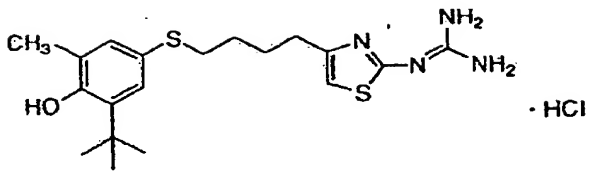
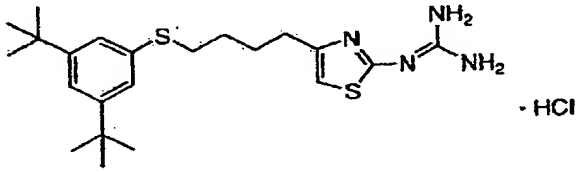
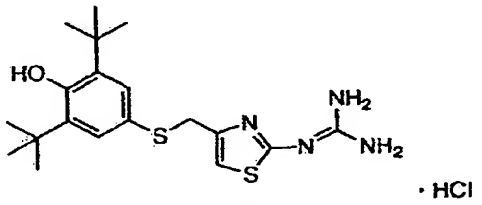


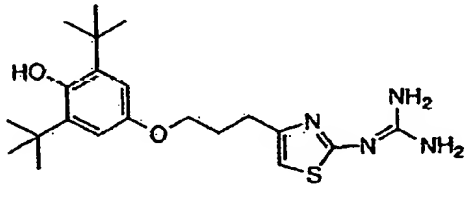
【０２４１】ＴＬＣ：Ｒｆ 0.42（酢酸エチル・酢酸：水＝２０：１：１）、
ＮＭＲ（$CDCl_3$）：δ 7.17(1H, d)，7.04(1H, d)，6.43(1H, s)，5.06(1H, s)，2.81(2H, t)，2.61(2H, t)，2.23(3H, s)，1.80-1.56(4H, m)，1.36(9H, s)。
【０２４２】実施例１（３７）
【化１２７】



【０２４３】ＴＬＣ：Ｒｆ 0.39（酢酸エチル：酢酸：水＝２０：１：１）、
ＮＭＲ（$CDCl_3$）：δ 7.24(1H, d)，7.18(2H, d)，6.45(1H, s)，2.95(2H, t)，2.65(2H, t)，1.85-1.65(4H, m)，1.31(18H, s)。
【０２４４】実施例１（３８）
【化１２８】



【０２４５】参考例１６で製造した化合物および相当するカルボン酸誘導体を用いて、参考例１９→参考例８→実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。
ＴＬＣ：Ｒｆ 0.57（クロロホルム：メタノール＝１０：１）、
ＮＭＲ（$CDCl_3$：CD_3OD＝１０：１）：δ 7.14(2H, s)，6.48(1H, s)，3.93(2H, s)，1.39(18H, s)。
【０２４６】実施例１（３９）
【化１２９】



【０２４７】参考例２０で製造した化合物を用いて、参考例２→参考例７→参考例８→参考例９→実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。

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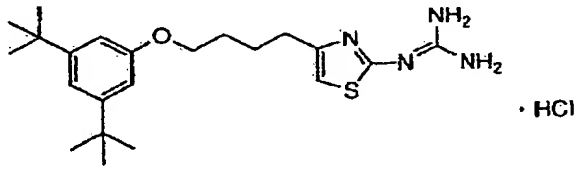
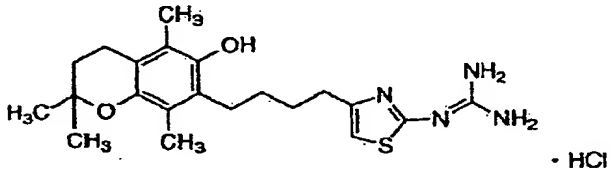
ＴＬＣ：Ｒｆ 0.35（酢酸エチル：酢酸：水＝２０：１：１）、
ＮＭＲ（$CDCl_3$）：δ 6.74(2H, s)，6.32(1H, s)，3.94(2H, t)，3.49(1H, s)，2.79(2H, t)，2.11(2H, m)，1.42(18H, s)。
【０２４８】実施例１（４０）
【化１３０】



【０２４９】相当する化合物を用いて、参考例２０→参考例７→参考例８→実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。
ＴＬＣ：Ｒｆ 0.40（酢酸エチル：酢酸：水＝２０：１：１）、
ＮＭＲ（$CDCl_3$＋CD_3OD（１滴））：δ 7.02(1H, d)，6.75(2H, d)，6.53(1H, s)，4.00(2H, t)，2.72(2H, t)，1.88-1.80(4H, m)，1.31(18H, s)。
【０２５０】実施例１（４１）～１（４３）
ＰＣＴ出願番号ＪＰ９５／２９４号明細書に記載されている化合物、７－（２－ホルミルエチル）－６－メトキシメチルオキシ－２，２，５，８－テトラメチルクロマン、５－（２－ホルミルエチル）－６－メトキシメチルオキシ－２，２，７，８－テトラメチルクロマンまたは８－（２－ホルミルエチル）－６－メトキシメチルオキシ－２，２，５，７－テトラメチルクロマンを用いて、それぞれ参考例５→参考例６→参考例７→参考例８→参考例９→実施例１と同様に操作して、下記の化合物を得た。
【０２５１】実施例１（４１）
【化１３１】



【０２５２】ＴＬＣ：Ｒｆ 0.55（クロロホルム：メタノール：酢酸＝１５：２：１）、
ＮＭＲ（CD_3OD）：δ 6.75(1H, s)，2.76-2.53(6H, m)，2.08(3H, s)，2.03(3H, s)，1.85-1.65(4H, m)，1.60-1.40(2H, m)，1.24(6H, s)。
【０２５３】実施例１（４２）
【化１３２】

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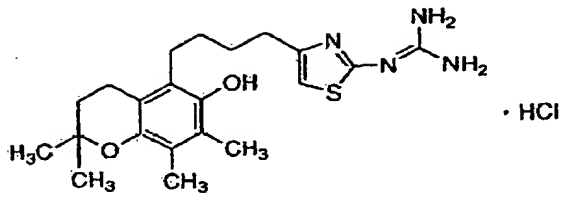
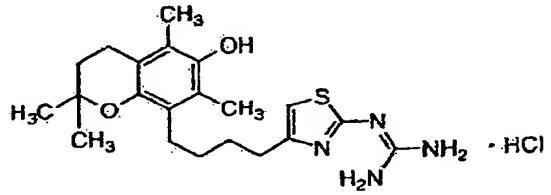
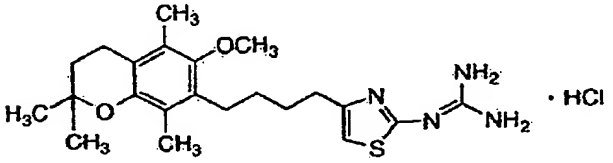


【0254】TLC：Rf 0.41（クロロホルム：メタノール：酢酸＝20：2：1）、
NMR（CD_3OD）：δ 6.75(1H, s)，2.77-2.53(6H, m)，2.12(3H, s)，2.04(3H, s)，1.85-1.67(4H, m)，1.60-1.40(2H, m)，1.26(6H, s)。
【0255】実施例1（43）
【化133】



【0256】TLC：Rf 0.37（クロロホルム：メタノール：酢酸＝20：2：1）、
NMR（CD_3OD）：δ 6.71(1H, s)，2.78-2.53(6H, m)，2.14(3H, s)，2.09(3H, s)，1.83-1.60(4H, m)，1.60-1.38(2H, m)，1.22(6H, s)。
【0257】実施例1（44）～1（46）
PCT出願番号JP95／294号明細書に記載されているかあるいはその明細書に記載の方法を用いて製造した化合物、7－（2－ホルミルエチル）－6－メトキシ－2，2，5，8－テトラメチルクロマン、5－（2－ホルミルエチル）－6－メトキシ－2，2，7，8－テトラメチルクロマンまたは8－（2－ホルミルエチル）－6－メトキシ－2，2，5，7－テトラメチルクロマンを用いて、それぞれ参考例5→参考例6→参考例7→参考例8→実施例1と同様に操作して、下記の化合物を得た。
【0258】実施例1（44）
【化134】



【0259】TLC：Rf 0.60（クロロホルム：メタノール：酢酸＝15：2：1）、
NMR（CD_3OD）：δ 6.73(1H, s)，3.62(3H, s)，2.78-2.55(6H, m)，2.12(3H, s)，2.04(3H, s)，1.86-1.67(4H, m)，1.60-1.40(2H, m)，1.27(6H, s)。
【0260】実施例1（45）
【化135】

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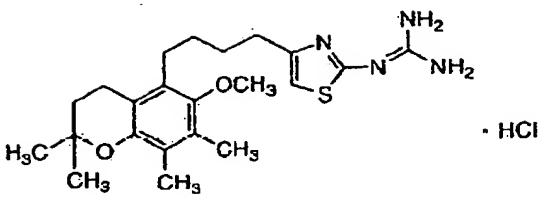
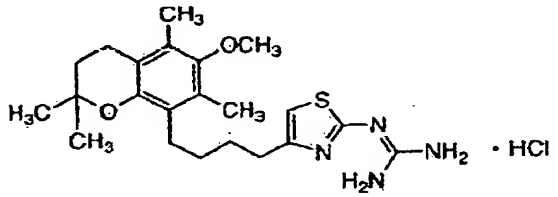
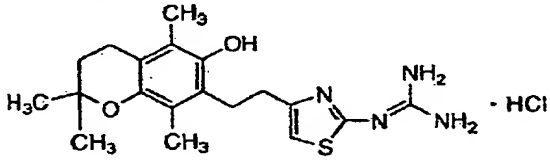


【0261】TLC：Rf 0.38（クロロホルム：メタノール：酢酸＝20：2：1）、
NMR（CD_3OD）：δ 6.76(1H, s)，3.61(3H, s)，2.78-2.53(6H, m)，2.14(3H, s)，2.04(3H, s)，1.83-1.65(4H, m)，1.62-1.38(2H, m)，1.27(6H, s)。
【0262】実施例1（46）
【化136】



【0263】TLC：Rf 0.37（クロロホルム：メタノール：酢酸＝20：2：1）、
NMR（CD_3OD）：δ 6.69(1H, s)，3.60(3H, s)，2.75-2.53(6H, m)，2.17(3H, s)，2.12(3H, s)，1.83-1.65(4H, m)，1.60-1.38(2H, m)，1.23(6H, s)。
【0264】実施例1（47）
【化137】



【0265】PCT出願番号JP95／294号明細書に記載されている、7－（2－メトキシカルボニルエチル）－6－メトキシメチルオキシ－2，2，5，8 テトラメチルクロマンを用いて、参考例8→参考例9→実施例1と同様に操作して、下記の物性値を有する標題化合物を得た。
TLC：Rf 0.43（クロロホルム：メタノール：酢酸＝15：2：1）、
NMR（$CDCl_3+CD_3OD$）：δ 8.31-8.03(1H, br)，6.74(1H, s)，3.07-2.91(2H, m)，2.91-2.72(2H, m)，2.62(2H, t)，2.12(3H, s)，2.08(3H, s)，1.80(2H, t)，1.28(6H, s)。
【0266】実施例1（48）
【化138】

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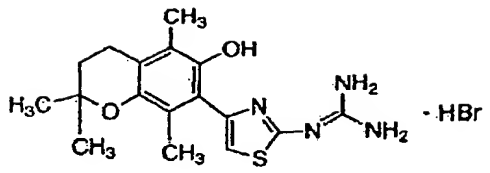


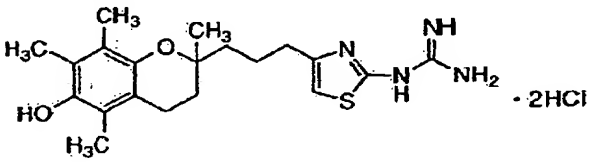
【０２６７】ＰＣＴ出願番号ＪＰ９５／２９４号明細書に記載されている、７－アセチル－６－メトキシメチルオキシ－２，２，５，８－テトラメチルクロマンを用いて、参考例１０→参考例１３→参考例１４→実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。

【０２６８】ＴＬＣ：Ｒｆ 0.56（クロロホルム：メタノール：酢酸＝３０：４：１）、

NMR (DMSO-d_6) ：δ 11.87(1H,brs), 8.17(4H,brs), 7.46(1H,brs), 7.15(1H,brs), 2.61(2H,t,), 2.06(3H,s), 1.87(3H,s), 1.76(2H,t), 1.25(6H,s)。

【０２６９】実施例１（４９）

【化１３９】



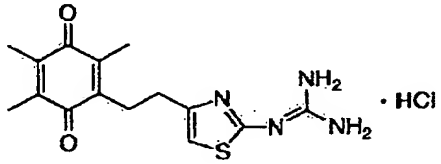
【０２７０】特開平３－２０４８７４号明細書に記載されている、２－（３－カルボキシプロピル）－２，５，７，８－テトラメチル－６－メトキシメチルオキシクロマンを用いて、参考例８→参考例９→実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。

【０２７１】ＴＬＣ：Ｒｆ 0.42（酢酸エチル：酢酸：水＝２０：２：１）、

NMR (DMSO-d_6) ：δ 12.30(1H,brs), 8.27(4H,brs), 7.37(1H,brs), 6.86(1H,s), 2.59(2H,t), 2.04(3H,s), 2.01(3H,s), 1.97(3H,s), 1.9-1.6(4H,m), 1.6-1.3(2H,m), 1.16(3H,s)。

【０２７２】実施例１（５０）

【化１４０】



【０２７３】参考例２１で製造した化合物を用いて、参考例８→実施例１と同様に操作して、下記の物性値を有する標題化合物を得た。

ＴＬＣ：Ｒｆ 0.51（酢酸エチル：酢酸：水＝１２：２：１）、

NMR (DMSO-d_6) ：δ 12.44(1H,brs), 8.29(4H,brs),

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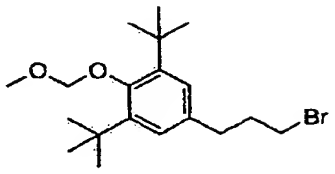
6.93(1H,s), 2.9-2.6(4H,m), 1.95(6H,s), 1.84(3H,s)。

【０２７４】参考例２６

【化１４１】

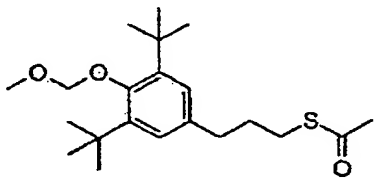


【０２７５】参考例３で製造した化合物を用いて参考例６と同様にして製造した、３－（３，５－ジ－ｔ－ブチル－４－メトキシメチルオキシフェニル）プロパノール（1.53ｇ）の塩化メチレン溶液（５０ｍｌ）に、トリフェニルホスフィン（1.57ｇ）、炭酸水素ナトリウム（1.26ｇ）および四臭化炭素（2.49ｇ）を加えた。混合物を室温で１時間撹拌した。反応混合物を酢酸エチルで希釈し、飽和炭酸水素ナトリウム、水および飽和食塩水で順次洗浄し、硫酸マグネシウムで乾燥後、濃縮した。残留物をヘキサン－酢酸エチルで洗浄し、得られたろ液を濃縮した。残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：１０）で精製して、下記の物性値を有する標題化合物（1.46ｇ）を得た。

ＴＬＣ：Ｒｆ 0.58（酢酸エチル・ｎ－ヘキサン＝１：１０）。

【０２７６】参考例２７

【化１４２】

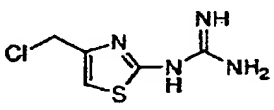


【０２７７】参考例２６で製造した化合物（1.46ｇ）のアセトン溶液（１０ｍｌ）に、チオ酢酸ナトリウム（６７６ｍｇ）を加えた。混合物を４時間還流した。反応溶液を冷却後、水に注ぎ、酢酸エチルで抽出した。有機層を水、飽和食塩水で洗浄し、硫酸ナトリウムで乾燥後、濃縮した。残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：３０）で精製して、下記の物性値を有する標題化合物（1.45ｇ）を得た。

ＴＬＣ：Ｒｆ 0.38（酢酸エチル：ｎ－ヘキサン＝１：１０）。

【０２７８】参考例２８

【化１４３】



【０２７９】アミジノチオウレア（1.68ｇ）のアセトン

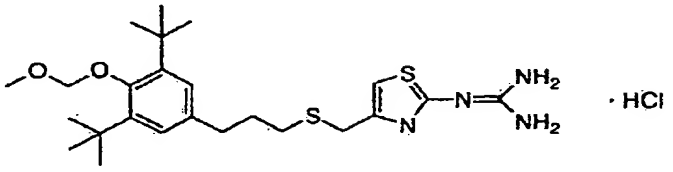
懸濁液（7.5ｍｌ）に、１，３－ジクロロアセトン（1.8ｇ）のアセトン溶液（６ｍｌ）を加えた。混合物を室温で一晩撹拌した。析出した結晶をアセトンで洗浄し、エタノールで再結晶し、下記の物性値を有する標題化合物（1.61ｇ）を得た。

＊ＴＬＣ：Ｒｆ 0.60（クロロホルム：メタノール：酢酸＝１５：２：１）。

【０２８０】参考例２９

【化１４４】

＊



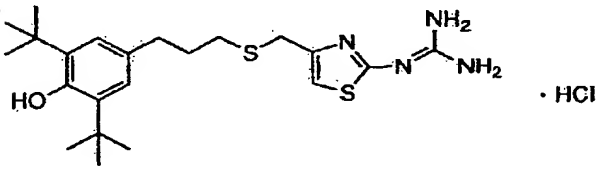
【０２８１】エタノール（５ｍｌ）に、ナトリウム（46ｍｇ）をアルゴン下で、少しずつ加え、溶解するまで撹拌した。調製したエトキシナトリウムのエタノール溶液に、参考例２７で製造した化合物（３６６ｍｇ）のエタノール溶液（５ｍｌ）を、０℃、アルゴン下で加えた。混合溶液を０℃で３０分間撹拌した。反応溶液に、参考例２８で製造した化合物（１１４ｍｇ）のエタノール溶液（５ｍｌ）をゆっくり滴下した。混合溶液を室温で３時間撹拌した。さらに、参考例２８で製造した化合物（１００ｍｇ）のエタノール溶液（５ｍｌ）を滴下した。混合溶液を室温で１６時間撹拌した。析出物を濾去し、ろ液を濃縮した。残留物をカラムクロマトグラフィ（クロロホルム：メタノール＝３０：１→１０：１）で精製して、下記の物性値を有する標題化合物（４８０ｍｇ）を得た。

【０２８２】ＴＬＣ：Ｒｆ 0.85（クロロホルム：メタノール：酢酸＝１５：２：１）、

NMR（$CDCl_3$）：δ 7.04(2H, s), 6.33(1H, s), 4.88(2H, s), 3.63(3H, s), 2.63(2H, t), 2.53(2H, t), 1.88(2H, quint), 1.78-1.55(2H, br), 1.43(18H, s)。

【０２８３】実施例２

【化１４５】



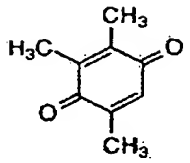
【０２８４】参考例２９で製造した化合物（４５０ｍｇ）を参考例９と同様に操作して、下記の物性値を有する標題化合物（４０８ｍｇ）を得た。

ＴＬＣ：Ｒｆ 0.30（クロロホルム：メタノール＝１０：１）、

NMR（DMSO-d_6）：δ 12.85(1H, br), 8.35(3H, brs), 6.95(1H, s), 6.88(1H, s), 6.70(1H, s), 3.73(2H, s), 2.60-2.43(2H, m), 1.35(18H, s)。

【０２８５】参考例３０

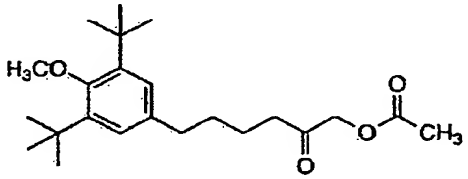
【化１４６】



【０２８６】２，３，５－トリメチルハイドロキノン（1.52ｇ）のＴＨＦ溶液（８０ｍｌ）に、水（８０ｍｌ）およびパラジウム（IV）アセテート（5.1ｇ）を加えた。混合物を３０分間加熱還流した。反応混合物に、２Ｎ水酸化ナトリウムを加え、エーテルで抽出した。有機層を水および飽和食塩水で洗浄し、硫酸マグネシウムで乾燥後濃縮して、標題化合物（1.32ｇ）を得た。

【０２８７】参考例３１

【化１４７】



【０２８８】参考例１１で製造した化合物を用いて、参考例７および参考例８と同様にして製造した、６－（３，５－ジ－ｔ－ブチル－４－メトキシフェニル）－α－クロロ－２－ヘキサノン（２００ｍｇ）および酢酸カリウム（１１１ｍｇ）のアセトン溶液（１０ｍｌ）を、６５℃で１７時間撹拌した。反応溶液を濃縮し、酢酸エチルで希釈した。有機層を水および飽和食塩水を洗浄し、硫酸マグネシウムで乾燥後、濃縮して、下記の物性値を有する標題化合物（1.32ｇ）を得た。

ＴＬＣ：Ｒｆ 0.33（ヘキサン：酢酸エチル＝５：１）。

【０２８９】実施例３

【化１４８】

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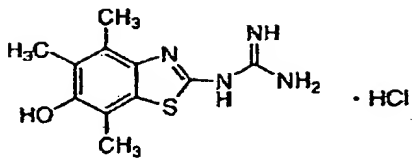


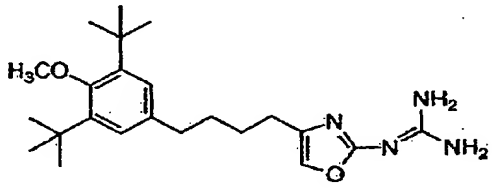
【０２９０】グアニジルチオウレア（５２０ｍｇ）のエタノール溶液（１０ｍｌ）に、濃塩酸（0.134ｍｌ）を加えた。混合物に、参考例３０で製造した化合物（1.32ｇ）のエタノール溶液（２０ｍｌ）を加えた。混合物を室温で２日間撹拌した。反応混合物をろ過し、結晶をアセトニトリルで洗浄した。ろ液を濃縮し、残留物をエタノールおよびエーテルで再結晶した。析出した結晶をアセトニトリル、エタノールおよびエーテルで順次洗浄し、乾燥して、下記の物性値を有する標題化合物（２５４ｍｇ）を得た。

【０２９１】ＴＬＣ：Ｒｆ 0.18（クロロホルム：メタノール＝５：１）、

ＮＭＲ（DMSO-d_6）：δ 12.6(1H,brs)，8.51(1H,s)，8.37(4H,s)，2.47(3H,s)，2.30(3H,s)，2.21(3H,s)。

【０２９２】実施例４

【化１４９】



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・４－（４－（３，５－ジ－ｔ－ブチル－４－ヒドロキシフェニル）ブチル）－２－グアニジルチアゾール　５．０ｇ
・繊維素グリコール酸カルシウム（崩壊剤）　０．２ｇ
・ステアリン酸マグネシウム（潤滑剤）　０．１ｇ
・微結晶セルロース　４．７ｇ

【０２９６】製剤例２

以下の各成分を常法により混合した後、溶液を常法により滅菌し、５ｍｌずつアンプルに充填し、常法により凍※結乾燥し、１アンプル中２０ｍｇの活性成分を含有するアンプル１００本を得た。

・４－（４－（３，５－ジ－ｔ－ブチル－４－ヒドロキシフェニル）ブチル）－２－グアニジルチアゾール　２．０ｇ
・マンニトール　２００ｍｇ
・蒸留水　５００ｍｌ

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＊【０２９３】参考例３１で製造した化合物（１７０ｍｇ）およびジシアンジアミド（３８０ｍｇ）のジオキサン溶液（９ｍｌ）に、５Ｎ塩酸溶液（1.8ｍｌ）を加え、室温で２０時間撹拌後、濃縮した。残留物をカラムクロマトグラフィ（酢酸エチル：ｎ－ヘキサン＝１：１０→５：１→クロロホルム：メタノール＝３０：１→１０：１）で精製して、下記の物性値を有する標題化合物（５１ｍｇ）を得た。

【０２９４】ＴＬＣ：Ｒｆ 0.50（クロロホルム：メタノール＝９：１）、

ＮＭＲ（$CDCl_3$）：δ 7.03(2H,s)，6.92(1H,s)，5.95(4H,brs)，3.67(3H,s)，2.55(2H,t)，2.45(2H,t)，1.67(4H,m)，1.42(18H,s)。

【０２９５】

【製剤例】

製剤例１

以下の各成分を常法により混合した後打錠して、一錠中に５０ｍｇの活性成分を有する錠剤１００錠を得た。

フロントページの続き

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// Ａ６１Ｋ	31/415	ＡＢＬ
		ＡＢＸ
		ＡＣＪ
		ＡＤＰ
		ＡＤＵ
		ＡＥＤ
	31/42	ＡＢＮ
	31/425	ＡＣＶ

Ａ６１Ｋ	31/415	ＡＢＬ
		ＡＢＸ
		ＡＣＪ
		ＡＤＰ
		ＡＤＵ
		ＡＥＤ
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	31/425	ＡＣＶ